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The Modern Pharmaceutical Industry: History, Current Position and Challenges

The development of modern medicine experienced a major leap forward in the nineteenth century because of advances in science and, since then, the evolution of scientific knowledge has pushed forward the growth of the modern pharmaceutical industry (Gribbin and Hook, 2004). The progress in human understanding of bacteriology and related subjects had replaced traditional knowledge of epidemiology and chemistry (Wikipedia, 2007a, "History of medicine"). The hygiene theory advocated by Ignaz Semmelweis (1818–1865) in 1847 paved the way for the germ theory of disease. The germ theory was put into practice later when, in 1865, British surgeon Joseph Lister discovered the principles of antisepsis (ibid.). The discoveries made by Louis Pasteur that pinpointed microorganisms as a major cause of diseases gave birth to a major conceptual breakthrough in the making of therapeutics. Against this background, Pasteur's invention of a vaccine against rabies in 1880 led to the success of other vaccine development (see Seppa, 18 and 25 December 1999). Pasteur's experiments, which confirmed germ theory, had important implications for using scientific method in the making of medicine. This method was articulated in Pasteur's book, *An Introduction to the Study of Experimental Medicine* in 1865. Pasteur and Robert Koch, who discovered tubercle bacillus in 1882, cholera bacillus in 1883, and Koch's postulates, founded bacteriology (Wikipedia, 2007a). These discoveries have paved the foundation for most modern pharmaceutical inventions.

In addition, genetic knowledge was advanced by Charles Darwin's publication of *The Origin of Species* in 1859 and Gregor Mendel's publication of a book in 1865 on Mendel's laws. Mendel's publication

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earned him the reputation of being the father of genetics (Gribbin and Hook, 2004; see also Darwin, 2003). Health sciences experienced another leap forward with discovery of the structure of DNA through the use of different models by Watson and Crick in 1953. These combined discoveries made a major contribution to the discipline of molecular biology and modern genetics (Watson, 2001). One of the most important contributions is that they provided a methodical, systematic framework for drug discovery.

On the whole, discoveries in bacteriology, genetics, and biochemistry have greatly advanced the use of scientific method in producing pharmacological products.

Drug development

A drug is defined as "a *chemical* substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being" (Dictionary.com Unabridged, v 1.1, 2007). The pharmaceuticals are synonymous with drugs, both of which denote the substances that have *medicinal* properties. Drug use varies with the nature of the diseases and the desired effects (The American Heritage Science Dictionary, 2007). The difference between drugs and hormones is that hormones are synthesized in the body while drugs are introduced into the body from outside.

Drug development requires some understanding of pharmacology. Pharmacology studies the interaction of drugs with living organisms to induce a change in function (Rang, 2006). Pharmacology entails the study of drug composition and properties, interactions, toxicology, therapy, and medical applications and antipathogenic capabilities (Wikipedia, 2007c, "Pharmacology"). Drug making also requires understanding both the pharmacokinetic properties of a drug in terms of absorption channels, distribution, metabolism/breakdown process, and excretion, and pharmacodynamics, such as knowledge of the therapeutic index (the chemical's toxic effect on the body) (ibid.). This knowledge dictates the choice of analogues as drug candidates. After a candidate drug is chosen, drug companies then launch a process of drug development to determine safety, stability, efficacy, and forms of dispensing (Newton, Thorpe and Otter, 2004).

The epistemological interaction between pharmacology and other disciplines has also broadened the knowledge of drug making. The subdisciplines of pharmacology include *clinical pharmacology*, the understanding of the medication effects on humans; *neuropharmacology* and

psychopharmacology, the study of the effects of medication on behavior and nervous system functioning; *pharmacogenetics*, the science of clinical testing of genetic variation giving rise to differential response to drugs; *pharmacogenomics*, the use of genomic technologies for new drug discovery and further characterization of older drugs; *pharmacoepidemiology*, the study of the effects of drugs at the population level; *toxicology*, the study of the effects of poisons; *posology*, the understanding of the dosing of medicines; and *pharmacognosy*, the science of the making of medicines from plants.

The pathway for drug development has undergone many changes since the nineteenth century but the goal has always been the same. That is, the drug development process aims to enhance efficacy (through the control of dosing and formulation) and safety (by controlling toxic levels and side-effects) (*Nature* Reviews Drug Discovery, July, 2006, "Editorial: Keeping sight of the goal"; see also Wikipedia, 2007b, "Pharmaceutical companies").

The inspiration for drug discovery relies either on knowledge of traditional ideas or "accidental" types of discoveries. The drug makers can isolate the active ingredient from traditional remedies or totally rely on chance for discovering the therapeutic effects of a drug (Schweitzer, 2006). The latter approach explains why only one out of 5000 potential candidate drugs will ever reach the open market (Newton, Thorpe and Otter, 2004). For example, the discovery of Viagra was fortuitous in the beginning stage of the process. In the late 1980s, some at Pfizer's laboratories in Sandwich, England, generated a hypothesis about the possible utility of a blocker against an enzyme called PDE5 to expand blood vessels and treat angina (Osterloh, June 2007). Later in the 1990s, following up on this hypothesis, a powerful and selective inhibitor of PDE5, known at the time as UK-92480, was developed. Early tests showed it had a moderate effect on the blood vessels of healthy volunteers, but its efficacy was short and it generated the side-effect of muscle aches. Coincidentally, in one of the studies, the drug had also generated the side-effect of increased erections for some subjects who received the treatment. While the scientists continued to pursue the possibility of using UK-92480 in combination with nitrates to treat angina, positive results for the drugs' potential in treating erectile dysfunction were being reported from the volunteers. Later, knowledge of the biochemical pathway related to erectile dysfunction directed drug development in a direction that aimed at amplifying the effects of the drug on the penal blood vessels. Clinical trials, which included those subjects with diabetes, helped further determine dosing levels to assure efficacy and

safety. The 1997 application for approval of Viagra resulted from an accidental discovery that led to eight years of drug research and four years of pilot studies.

Beyond the serendipity-based approach, increasingly drug development has benefited from the advancement of molecular biology and biochemistry (Larson, 2005). Molecular analysis of the biochemical processes and properties of cells and their functions has revolutionized the pharmaceutical industry. Modern biotechnology makes it possible to understand the metabolic pathways causing a disease. Understanding the functions of receptors renders it possible to design chemicals that manipulate the metabolic pathways so that they achieve a desired effect on cell-surface receptors that could affect cell functions (Wikipedia, 2007b).

The history of large pharmaceutical companies

Scientific breakthroughs and legislative initiatives have paved the way for large, modern pharmaceutical companies. The discovery of effective cures, such as insulin and penicillin in the 1920s and 1930s, was not only instrumental in improving population health but has also created a unique economic sector. The large pharmaceutical companies have mainly originated from Switzerland, Germany, Italy, the United Kingdom, and the United States (Nelson, 1983). Legislative improvements that facilitate the growth of the industry include quality and safety control, appropriate labeling, and separation of prescription from nonprescription drugs. The advances in pharmaceutical-related sciences, such as in molecular biology, led to fruitful results in the 1950s and 1960s, which were considered the beginning of the gilded age in drug discovery. A large number of effective pharmaceuticals were invented and produced. These include the invention of the first oral contraceptives; blood-pressure drugs and heart medications; and psychiatric medications (MAO Inhibitors), chlorpromazine (Thorazine), Haldol (Haloperidol), the tranquilizers, and Valium (diazepam) (Wikipedia, 2007b). In the 1970s, cancer treatment became a major focus of drug development (ibid.).

The need for regulatory oversight over pharmaceutical safety heightened in the 1960s because of the occurrence of certain life-threatening incidents. The most serious was the use of Thalidomide, which was causing birth defects among many infants. In the 1970s, the industry began to expand and was on its way to becoming a mega-industry. In the mid-1980s, horizontal and vertical integration led to the emergence

of large multinational pharmaceutical companies. Strategic partnerships were formed between large pharmaceutical companies and small biotechnology firms. Mergers and corporate buyouts among competitors also expedited this trend.

The high-growth scenario experienced a change in the 1980s. Increasingly, the industry was facing barriers in innovation, regulatory pressure, and the need to address global health challenges. There was an urgent need to create effective drugs for HIV/AIDS that could be accessed by a large number of the resource poor populations in developing countries. Despite the breakthrough in the invention of useful drugs for heart disease that became a major source of profit for pharmaceutical companies at the time, the world intensified their criticism of the industry. The AIDS crisis has also made the world pay attention to the pricing controversy in the pharmaceutical industry. In a related development, the need to contain health care cost in the United States has also attracted the public's attention to the affordability issue of pharmaceuticals.

In the 1990s, with the aid of advancements in science and technology, the industry was growing at a new level and continued the vertical and horizontal integration momentum by involving a larger number of partners in the drug development process. Its partners include research institutes in the public sector, such as the National Institutes of Health (NIH) in the United States, and academia, which started playing an increasing role in the basic research stage of drug development. The outlets for pharmaceutical sale have also increased. The emergence of internet pharmacy during this time has effected quality control, pricing and large pharmas' marketing strategies and could pose a threat to the bottom line of the business. On the other hand, in the United States, direct-to-consumer advertising on radio and TV gave the pharmaceutical companies greater access to influencing consumers directly because of a more liberal approach adopted by the US Food and Drugs Administration (FDA), as a result of new regulations in 1997 in the presentation of pharmaceutical risks. Drug development during this time became more methodical and systematic. The "hits" included the new antidepressants (the SSRIs), especially the Prozac (Fluoxetine), Viagra, and new AIDS drugs. In addition to competition from complementary medicine and nutritional supplements, the industry was also facing uncertainty about the safety of newer drugs. For example, the Vioxx controversy put tremendous pressure on the regulatory agencies and the industry to improve the drug development process.

The first decade of the new millennia witnessed increasing dynamic and aggressive expansion and continuous consolidation of the industry.

It is noted that the pharmaceutical sector, composed of more than 200 major pharmaceutical companies, is one of the most profitable industries (USA Today, 2002, "How to buy prescription drugs at over 50 percent off US price"). The proliferation of new and intractable diseases has rendered this industry even more opportunities than before. Advances in the sciences, especially in biotechnology and genetics, have produced major breakthroughs in the discovery and making of medicines, such as gene therapy or individualized medicine. In the United States, the industry has also become one of the most politically influential players, as evidenced by the employment of the largest troop of lobbyists on Capital Hill (Center of Public Integrity, 7 July, 2005). A report by the Center of Public Integrity showed that between 1998 and 2005, the pharmaceutical and health products industry spent more than $800 million in federal lobbying and campaign donations at both federal and state levels – which effort was considered to be the largest in the United States during that period. These developments have alerted their critics. Scrutiny and criticism of the industry, targeting such issues as manipulation of pricing, insensitivity to the needs of the developing world, inflating efficacy claims and disease mongering, and lack of innovation, has also intensified (ibid.). As critics are increasing their scrutiny, so linkages between the industry and regulator are exposed to the public. Nevertheless, throughout the history of pharmaceutical development, the regulatory bodies in developed markets have in general played a positive role.

Regulatory environment

As mentioned in Chapter 1, the regulatory bodies play a major role in overseeing the approval, manufacturing, sales and marketing, consumption, and surveillance of pharmaceuticals. Among all the regulatory bodies in the world, the FDA in the United States, a scientific, public health and regulatory agency, is a major operational model for other countries.

The FDA has undergone tremendous growth since 1862, when it was the Division of Chemistry with a single chemist in the US Department of Agriculture (Swann, 2007, "History of FDA"). These days, with a budget of $2.4 billion in 2008, the FDA is equipped with a staff of approximately 9100 employees, including chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. About one-third of the agency's employees are stationed outside of the Washington, DC, area, operating in 150 field offices and

laboratories, including five regional offices and 20 district offices (AAAS, 2008; Swann, 2007). The items under the charge of FDA encompass most food products (other than meat and poultry); human and animal drugs; therapeutic agents of biological origin; medical devices; radiation-emitting products for consumer, medical, and occupational use; cosmetics; and animal feed.

The transformation of FDA from a Bureau of Chemistry in 1901 to the guardian of American consumption of health-related products was due to a number of historic accidents, incidents, and landmark legislation. The 1906 passage of the Federal Food and Drugs Act increased the FDA's regulatory functions. The Bureau of Chemistry was changed to the Food, Drug, and Insecticide Administration in July 1927, when the agency focused its role on the regulation and transfer of non-regulatory research functions to other agencies in the department. FDA's current name derives from a change made in July 1930. In June 1940, the agency was transferred to the new Federal Security Agency, but was moved back again to the Department of Health, Education, and Welfare (HEW) in April 1953. The FDA became part of the Public Health Service within HEW in 1968, and then in May 1980, FDA was placed under the Department of Health and Human Services, when HEW was renamed after removing its education function.

The evolution of the FDA has to do with the role of federalism in harmonizing approaches to inconsistent and unsafe food and drug-making practices. Some states, such as Massachusetts, were more progressive or protective than others. The FDA's short-lived enforcement of the Vaccine Act of 1813 was the first federal law attempting to harmonize consumer protection and therapeutic substances. Before the FDA was able to assert its authority, the states had the most control over the production, sale, and transportation of food and drugs. Federal authority was limited mostly to imported foods and drugs. However, at the time, unethical and inauthentic practices, such as adulteration and misbranding of foods and drugs, were prevalent and aggravating in the late nineteenth century. Drug safety was of particular concern to the public when, at the time, even ethical companies engaged in making "unethical medicine," such as by diluting quinine-containing cinchona bark powder with such other ingredients as alum, or using clay to mask poor wheat flour (Swann, 2007). The unethical practices increased profits for these companies, but took a toll on the health of the public.

In 1867, the lack of enforcement against misbranding and adulteration by the federal agency, forced a change in the Division of Chemistry at the public's demand (Swann, 2007). The arrival of Harvey W. Wiley

in Washington as chief chemist in 1883 heralded a major change in FDA's public role (*FDA Magazine*, 2006). Widely lauded as a pioneer consumer activist, Wiley W. Harvey, a Harvard graduate, pushed the agency to start taking an active role in protecting the safety of the public in the consumption of food and drugs. By first publishing the division's research in this area in a ten-part study, *Foods and Food Adulterants*, conducted from 1887 to 1902, Harvey raised his concern about the "poison squad" experiments, the ancient version of unsupervised "clinical trials," in which able-bodied volunteers consumed varying amounts of questionable food additives to determine their impact on health. To address this dangerous practice, Harvey, with the support of state chemists and food and drug inspectors, the General Federation of Women's Clubs, and national associations of physicians and pharmacists, tried to enforce a federal law to prohibit the adulteration and misbranding of food and drugs.

Since then, the US Food and Drug Administration has a large influence on the US economy. It is noted that the $1 trillion worth of products monitored by the FDA is at a cost to taxpayers of about $3 per person per year. In another estimate, the items under the charge of US FDA account for 25 cents of every dollar spent by consumers (Swann, 2007).

Major legislations on pharmaceuticals

There are several legislations that form the backbone of the regulatory framework for pharmaceuticals sold in the United States and some of these standards have been used by other countries. In the United States, the major legislative effort was the 1906s Food and Drugs Act, or the Wiley Act, signed by President Roosevelt (US Department of Health and Human Services, 2007, "The 1906 Food and Drugs Act and Its Enforcement"). This Act prohibited the interstate transport of unlawful food and drugs under penalty of seizure of the questionable products and/or prosecution of the responsible parties. The basis of the law rested on the regulation of product labeling rather than pre-market approval. Drugs, defined in accordance with the standards of strength, quality, and purity in the US Pharmacopoeia and the National Formulary, could not be sold in any other condition unless the specific variations from the applicable standards were plainly stated on the label (ibid.).

In the wake of a therapeutic disaster in 1937, which caused more than 100 casualties due to the use of the "claimed" wonder drug Elixir Sulfanilamide, the Food, Drug, and Cosmetic Act was passed in 1938. The new law brought cosmetics and medical devices under control, and

it required that drugs be labeled with adequate directions for safe use. Moreover, it mandated pre-market approval of all new drugs, so that a manufacturer would have to prove to FDA that a drug was safe before it could be sold. This act irrefutably prohibited false therapeutic claims for drugs, although a separate law granted the Federal Trade Commission jurisdiction over drug advertising. The act also corrected abuses in food packaging and quality by mandating legally enforceable food standards. Tolerances for certain poisonous substances were addressed. The law formally authorized factory inspections, and it added injunctions to the enforcement tools at the agency's disposal (US Department of Health and Human Services, 2007).

Other important legislation includes: In 1951, Congress passed a law requiring the use of doctors' prescriptions to buy drugs and in 1961, a law dictating that drugs have to show efficacy in addition to the safety standard.

Several legislations passed in the 1980s and 1990s have a far-reaching impact on the process of clinical development and regulatory review of new therapeutics in the United States. For example, the Bayh-Dole and Stevenson-Wydler Act facilitated technology transfer between research institutions and industries, including the pharmaceutical makers (Franklin Pierce Law Center, 2008, "Overview of federal technology transfer"). This Act allows small businesses and non-profit organizations a statutory right to choose to retain title to inventions made during federally assisted research and development (R&D) so long as they were interested in patenting and attempting to commercialize those inventions. To be more specific, under this Act, the universities can patent discoveries from NIH-sponsored research, and then grant licenses to pharmaceutical companies. It was believed that this Act increased technology transfer from public-sector resources to private sector, inducing a major impetus for the growth of the biotechnology sector and the large pharmaceutical companies (US Government Technology Administration, 9 May 2002; see also Franklin Pierce Law Center, 2008). The Orphan Drug Act, signed into law on 4 January 1983, was another attempt to stimulate the research, development, and approval of products that treat rare diseases, defined as diseases affecting fewer than 200,000 Americans (FDA, 1983, "Orphan Drugs"). The mechanisms to support the act include: marketing exclusivity for the drug's sponsors after the orphan drug product is approved; tax incentives for clinical research undertaken by the sponsors; assistance from FDA's Office of Orphan Products Development to coordinate research study design by the sponsors; support from the Office of Orphan Products Development for sponsors to

conduct open protocols, allowing patients to be added to ongoing studies; and availability of grant funding to defray costs of qualified clinical testing expenses incurred in connection with the development of orphan products. It is noted that since the passing of Orphan Drug Act, over 100 orphan drugs and biological products have been brought to market. In 1984, the US Congress passed the Hatch-Waxman Act, or the Drug Price Competition and Partner Term Restoration Act. This law has also facilitated the growth of the industry. This Act was revised in 2000, when cross-border pharmaceutical purchases were liberalized. In this revision, Americans could buy back FDA-approved drugs from Canada (Angell, 2004). This is an improvement of a 1987 law passed by the US Congress that illegalized cross-border purchases of prescriptions by American citizens other than the manufacturers. In 1992, came the Prescription Drug User Fee Act, authorizing drug companies to pay user fees for drug evaluations to the FDA.

The legislation of the Food and Drug Administration and Modernization Act of 1997 is designed to address an unmet medical need. It applies to the combination of a product and a claim seeking FDA approval (FDA, 1997, "Food And Drug Administration and Modernization Act Of 1997"). This act was designed for fast track approval and is independent of Priority Review and Accelerated Approval. The benefits of the Fast Track law include FDA input in the development process in the form of scheduled meetings; the option of submitting a New Drug Application in sections without having to submit all components simultaneously; and the option of requesting evaluation of studies using surrogate endpoints. This Act also allows one clinical trial, instead of two. Under this legislation, pharmaceutical makers are not required to test the new drugs against the old ones, which opens the door for "me-too" drugs. This allows US Medicaid program to pay for off-label uses after decisions by three private organizations (Angell, 2004).

The new FDA regulations in 1997 aroused some criticism because they were thought to have liberalized requirements for the presentation of risks in the direct advertisements to pharmaceutical consumers (Angell, 2004). Instead of having to present a comprehensive list of risks, this legislation allows the companies to list only major risks and to refer viewers to a source of additional information. This act was believed to have contributed to the rise in drug sales. For example, the new antidepressants, or the SSRIs, such as Fluoxetine (Prozac), rapidly became bestsellers and were marketed for additional disorders (ibid., 2004).

Pressure from the public to lower medicines led to the opening up of the pharmaceutical market (American Medical Student Association, 13 April 2008, "Prescription drug importation: A short-term effort to reduce drug prices"). As mentioned earlier, in 2000, the US Congress passed legislation allowing the re-importation of pharmaceuticals on condition that there was assurance of safety from the Secretary of Health and Human Services, with the advice of the FDA.

Global regulatory framework

In the global context, one of the most important policy guides was the issuance by the World Medical Association of the 1964 Declaration of Helsinki (The World Medical Association, 2004, "Declaration of Helsinki"). This declaration sets standards for clinical evaluations by demand that informed consent be obtained from clinical trial subjects before enrollment in an experiment. Pharmaceutical companies were mandated to prove efficacy in clinical trials before they could market their drugs.

On the issue of intellectual property rights, in the 1970s the legislation GATT (the General Agreement on Tariffs and Trade) allowing for strong patents, to cover both the process of manufacture and the specific products, came into force on the global scene (Wikipedia, 2007b). In late 1990s, the World Trade Organization set out to harmonize protection of intellectual property rights for traded goods, including pharmaceuticals, through the enactment of TRIPS (Trade-Related Aspects of Intellectual Property Rights). This global trade regulation is instrumental in facilitating the large pharmaceutical companies to expand their global frontiers, with far-reaching implications on global health.

Pharmaceutical companies

The modern pharmaceutical industry would not exist were it not for some innovative nineteenth-century pioneers, who laid the foundations for the development of large multinationals today.

Eli Lilly. One of these pioneers was Colonel Eli Lilly, the founder of Eli Lilly Pharmaceuticals. He started his career in 1854 as a 16-year-old intern in an Indiana apothecary shop, equipped with mortars, pestles, rows of gleaming glass flasks, and ceramic apothecary jars (Eli Lilly Company, 2007, "History"; Bioanalytical Systems Inc., 2007e, "The pharmaceutical industry: A history and calendar"). When Lilly himself opened his shop on 10 May 1876, his staff of three included a drug

compounder, a bottler and finisher, and his 14-year-old son Josiah K. Lilly, Sr. In this traditional setting, herbs, roots, minerals, oils, and other materials were the sources of medicines.

Eli Lilly's new company in 1876 offered the so-called "ethical" medications, when other companies produced such medicines as were brewed and peddled by slick hucksters. These "ethical" medications were dispensed only on the advice of authentic physicians. His first products in herbal preparations, extracted from Bear's Foot, Black Haw, Cramp Bark, Hardhack, Life Root, Skullcap, Sea Wrack, Squaw Vine, Wahoo, and Wormseed, were reputed for their quality and the generosity and community spirit of the company's founder. The major product of the company was insulin, which Eli Lilly & Company co-developed with Canadian physician Frederick Banting in 1921. This discovery was based on observation by Banting and graduate student Charles Best in experiments showing that animal pancreas extractions were able to regulate sugar metabolism in diabetic dogs. Another improvement in insulin production was made in 1922, when Lilly scientists invented the iso-electric precipitation procedures to increase manufacturing yields and improve the purity, potency, and stability of insulin product. In 1923, Iletin was registered as the first commercial insulin from Eli Lilly and Company (Bioanalytical Systems Inc., 2007b, Eli Lilly and Company).

Merck. The other early pioneer was Merck, one of the oldest chemical and pharmaceutical companies in the world. Merck and Company was founded in 1668 when Friedrich Jacob Merck, an apothecary, bought out the "Engel-Apotheke" in Darmstadt, Germany (see Merck and Company, 2002, "History"). After 1816, Merck began to manufacture bulk quantities of alkaloids, plant extracts and other chemicals and in 1888, Merck had started selling guaranteed pure reagents to the market.

Merck continued to expand in the turn of the nineteenth century (Bioanalytical Systems Inc., 2007d, "Merck and Company"). In 1891, Merck and Co., under George Merck who was grandson of Emanuel Merck, started increasing Merck's presence in the United States by presiding over the New York office. In 1902, Merck began to produce such fine chemicals as bismuths, iodides, and narcotics (including morphine and cocaine). Merck's mergers in 1927 with chemical producer PWR and in 1953 with pharmaceutical company Sharp & Dohme made the company focus on the business of pharmaceutical research. Since the 1970s, Merck has introduced Sinemet to treat Parkinson's disease;

Timoptic to treat glaucoma; Heptavax-B vaccine to treat hepatitis B; and Zocor and Mevacor to treat cholesterol. Zocor and Mevacor today control about 40 percent of the world market. In addition, the company produced the top-selling Vasotec for hypertension, Crixivan for AIDS treatment, and Propecia (for baldness) (ibid.). Today, Merck & Co., Inc. is a leading pharmaceutical producer with 70,000 employees in 120 countries and 31 factories worldwide and their products are sold in more than 200 countries (see Merck and Company, 2002).

Bayer. Bayer started making its name in pharmaceutical history when the precursor of aspirin was invented (Bayer, 2007, "Bayer: Science for a better life"). The general partnership "Friedr. Bayer and company," founded on 1 August 1863 in Barmen, Germany, by dye salesman Friedrich Bayer (1825–1880) and master dyer Johann Friedrich Weskott (1821–1876) paved the way for a very successful pharmaceutical business. In 1881, Bayer was transformed into a joint stock company "Farbenfabriken vorm, Friedr. Bayer & Co." On 10 August 1897, Dr Felix Hoffmann, a chemist in Farbenfabriken vorm, part of Friedr. Bayer & Co., successfully acetylated salicylic acid into a chemically pure and stable form of acetylsalicylic acid (ASA) that could be used to relieve rheumatic pain; ASA is the active ingredient for aspirin. Introduced in 1899, aspirin is the best-known and most frequently used medicine in the world. In 1915, aspirin, the first drug in tablet form, was available without a prescription. The benefits of the drug far extended its original purpose. Today, its therapeutic effects include the possible prevention of heart attacks and colon cancer. Bayer also discovered polyurethane chemistry in the 1930s and developed the first broad-spectrum antimicrobial for treatment of fungal diseases in humans (Bioanalytical Systems Inc., 2007a, "Bayer corporation").

Bristol-Myers Squibb. Bristol-Myers Squibb has become a dominant player in the sector after a merger with the Squibbs in 1989, one of largest single stock transfers in the history of the health care industry (Bristol-Myers Squibb, 2006, "A Brief History of Bristol-Myers Squibb"). The new company became the second largest in the pharmaceutical sector.

The company started out in 1887 when William McLaren Bristol and John Ripley Myers put their investment of $5000 into a failing drug manufacturing company named the Clinton Pharmaceutical Company, Clinton, New York. On 13 December 1887, the company was officially incorporated (ibid.). The initial $5000 investment has grown into a $12 billion diversified global health and personal care company with more

than 47,000 employees worldwide and thousands of products marketed in more than 130 countries.

Bristol-Myers Squibb Worldwide Pharmaceuticals is reputable for therapies for cardiovascular, metabolic and infectious diseases, central nervous systems and dermatologic disorders, and cancer. The research arm of the company, the Bristol-Myers Squibb Pharmaceutical Research Institute, was established to engage in research in oncology, cardiovascular and metabolics, anti-infectives, neurosciences, immunology and inflammation, dermatology, and pain management (Bristol-Myers Squibb, 2006). The better known products include treatments for HIV and cancer. For example, in 1991 the company's Videx® (didanosine), or ddI, was second only to AZT as the most used medicine available for treating HIV infection. In the same year, the company's Cooperative Research and Development Agreement with the National Cancer Institute led to the development of a new compound, TAXOL® (paclitaxel). TAXOL, derived from the bark of the endangered Pacific Yew tree, was found to be effective in treating cancer. Since its launch in 1993, TAXOL has become one of the world's most widely used cancer treatments; ibid.).

Pfizer. Pfizer, a leading player in the pharmaceutical industry, is always associated with penicillin as its most famous drug (Pfizer, 2008a, "About Pfizer"). Penicillin, discovered by bacteriologist Alexander Fleming in 1928, was not mass produced until Pfizer used the technique of deep-tank fermentation to produce penicillin in the 1940s. By 1944, Pfizer was the largest producer of penicillin in the world (Bioanalytical Systems Inc., 2007f, "Pfizer"). Today, Pfizer is widely known for its innovative new drugs. For example, Geodon® (ziprasidone hydrochloride) is a new antipsychotic for the treatment of schizophrenia; Relpax® (eletriptan HBr) was developed specifically for the treatment of migraines; Exubera® (insulin human [rDNA origin]) Inhalation Powder is the first diabetes treatment for adults with Type 1 and Type 2 diabetes that can be inhaled (ibid.). Beyond its pharmaceutical leadership, it is widely known for its participation in global health partnerships to improve health in developing countries, such as the Diflucan® Partnership Program, a member of the UN Global Compact, and its HIV/AIDS Health Literacy Grants Program.

Hoechst. Hoechst AG is the world's largest chemical manufacturer with businesses in 120 nations around the globe and since the mid-1990s, most of its revenue, more than 75 percent, derives from foreign sale

(Hoechst, 2008, "Hoechst A.G."). Hoechst Marion Roussel is the pharmaceutical company of Hoechst AG and its major products include therapies for allergic, metabolic, and central nervous systems disorders and cardiovascular and infectious diseases (see Pfizer Inc., 2008b, "Pfizer Inc and Hoechst Marion Roussel to Co-Develop and Co-Promote Inhaled Insulin").

Hoechst Marion Roussel, with roots in its aniline dye factory in 1863 at Höchst am Main, Germany, introduced its first pharmaceutical product, Antipyrin, in 1883 as the world's first safe and effective synthetic painkiller and the first drug to leave the factory in a ready-dosaged and packaged form. Other important products included tuberculin (1892), diphtheria and tetanus antitoxins (1894 to 1897), and Novocain®, the first safe local anesthetic (1905). Its Salvarsan®, discovered in 1910, was the first effective treatment for syphilis and the inception of chemotherapy. A leader in research in diabetes, Hoechst helped produce the first insulin in Europe in 1923, and it also went on to introduce products to improve tolerability, such as crystalline insulin and the popular oral hypoglycemics Orinase® and DiaBeta®.

Hoechst's acquisitions of other companies have also expanded its business profiles. In 1995, Hoechst's acquisition of Marion Merrell Dow, which was known for the production of calcium supplementation, Os-Cal®, made of oyster shells, the Cardizem family of cardiovascular drugs, the non-sedating antihistamine Seldane, and Carafate, an anti-ulcer product. In 1997, Hoechst acquired Roussel Uclaf, which, created in 1929, had produced Hemostyl, an anti-anaemia product, and was one of France's most important pharmaceutical companies. Roussel Uclaf, which built its first fermentation plant in 1946, had developed such breakthrough antibiotic products as Cefotaxime, a third-generation cephalosporin (1981), and the macrolide antibiotic Roxithromycin (1987). By the 1990s, this French company held 10,000 patents worldwide (Bioanalytical Systems Inc., 2007c, Hoechst Marion Roussel).

Glaxo-Smith-Kline (GSK). Glaxo-Smith-Kline combines the history of a number of pharmaceutical leaders, such as Glaxo, Wellcome, Affymax (a leader in the field of combinatorial chemistry), and Smith-Beecham-Kline. Today, GSK has 7 percent of global market share and produces medicines that treat asthma, virus control, infections, mental health, diabetes, and digestive conditions. It is a major stakeholder in vaccines and cancer treatments (GSK, 2007, "Our company"). GSK's other products include over-the-counter (OTC) medicines, such as Gaviscon and

Panadol; dental products such as Aquafresh and Macleans; smoking control products Nicorette/Niquitin; and nutritional health care drinks such as Lucozade, Ribena and Horlicks.

The founding of Smith-Beecham-Kline could be traced back to the combination of three individual pharmaceutical pioneers in the nineteenth century. The founder of Beecham, a shepherd boy in the 1820s, started his pharmaceutical business based on his observation of the medicinal properties of the vegetation consumed by his sheep. His observation led to the production of "Beecham's Pills," which reached a million tablets each day by 1913. The company made its mark in the 1950s with the discovery of 6-APA, the form of the penicillin nucleus important in suppressing resistant strains of infectious disease.

In 1830, John K. Smith founded an apothecary shop in Philadelphia and delved into the drug wholesale business as a result of a partnership in 1865. The company, renamed Smith, Kline and French, after a merger with French Richards and Co., was Philadelphia's leading drug vendor, selling hundreds of products, including tonics, medicines, liniments, and perfumes. The company ventured into new medicines after the 1929 Wall Street crash. The company made its mark by developing Benzedrine for nasal congestion; Dexedrine for treating obesity; and Thorazine for mental illness. Its inventions of capsules that allow the release of medicine over an extended period of time together with Tagamet for treating peptic ulcers were among some of its well-known achievements. Tagamet was a blockbuster with sales reaching an all time high of $1 billion.

Today's SKB has derived from several mergers. The merger between Smith Kline Beckman in the United States and the Beecham Group in the United Kingdom in July 1989 created SmithKline Beecham, and its core products include prescription medicines, vaccines, consumer health care products, and the business of clinical testing in the world (Bioanalytical Systems Inc., 2007g, "SmithKline Beecham"). In 1995, Glaxo and Wellcome merged to form Glaxo Wellcome. Then, Glaxo Wellcome acquired California-based Affymax, a leader in the field of combinatorial chemistry. In 2001, GlaxoSmithKline was formed as a result of the merger of Glaxo Wellcome and SmithKline Beecham (ibid.).

Wyeth. A company incorporated as "American Home Products" (AHP) in 1926 became Wyeth in 2002 (Fundinguniverse, 2008, "Wyeth"). American Home Products were associated with such popular products as Black Flag insecticides, Easy-Off oven cleaner, Woolite, and Chef

Boyardee, and familiar pharmaceuticals like Anacin, Advil, Dristan, Robitussin, and Dimetapp. A global operator, Wyeth develops and markets traditional pharmaceuticals, vaccines, and biotechnology products, such as over-the-counter (OTC) medications and nutritional supplements. Its clients spread to more than 140 countries, and it has manufacturing facilities on five continents. During the 1990s, the company started focusing on medicine and pharmaceuticals by selling off other businesses. In 2002, the company changed its name from American Home Products to Wyeth. In fact, AHP had already acquired Wyeth Chemical Company (now Wyeth Laboratories) in 1932.

Wyeth Laboratories, the core of today's Wyeth-Ayerst Pharmaceuticals that began in Philadelphia, Pennsylvania, was founded by brothers John and Frank Wyeth in a drug store in 1860. The brothers were pioneers in pharmaceutical supply chain management. John was a pioneer in preparing frequently prescribed compounds in advance, and later, they published a catalog listing their line of drug preparations, elixirs, and tonics. A counterpart, Ayerst, McKenna & Harrison, Ltd., established in 1925 in Montreal, Canada, became the first commercially operated biological laboratory in Canada when the company was trying to produce a biologically tested cod liver oil (Bioanalytical Systems Inc., 2007h, "Wyeth Ayerst"). After Wyeth in 1866 absorbed A. H. Robins, a former apothecary and manufacturing chemist shop in Richmond, Virginia, it acquired a broad line of prescription medications. Wyeth also included Lederle Laboratories, founded in New York in 1906 by Dr Ernst Lederle, a pioneer in the fight against disease among children, and was known for its invention of diphtheria antitoxin.

Wyeth made its name in developing the "compressed pill," or tablet. The first rotary tablet press was also invented by Wyeth in 1872. Other products include an infant formula patterned after mother's milk; the first orally active estrogen (which became the pioneer product for estrogen replacement therapy); the first penicillin tablets and oral suspensions; and development of a heat-stable, freeze-dried vaccine and the bifurcated needle used to deliver 200 million smallpox vaccinations per year.

These aforementioned companies were among some of the oldest pharmaceutical businesses that laid the foundations for today's larger pharmaceutical companies. In 2006, the top large pharmaceutical companies in terms of market share were: Pfizer (7.2 percent), GlaxoSmith-Kline (5.9 percent), Sanofi-Aventis (5.7 percent), Novartis (4.6 percent), Hoffmann-La Roche (4.2 percent), AstraZeneca (4.1 percent), Johnson & Johnson (3.7 percent), Merck & Co. (3.6 percent), Wyeth (2.5 percent), and Eli Lilly (2.4 percent). These top ten dominated global sales of

pharmaceuticals in 2006. The fastest rate of growth was experienced by Hoffmann-La Roche with 21.8 percent, followed by Novartis' 18 percent, AstraZeneca's 10.5 percent, and GSK's 9.7 percent (Ebisch, March 2005, "Prescription for change"; see also Wood McKinzie Productview, March 2007). The top ten pharmas are followed by Bristol-Mers Squibb, Amgen, Abbott, Boehringer-Ingelheim, Takeda, Bayer Schering, Schring-Plough, Astellas Pharma, Daiichi-Sankyo, Novo Nordisk, Eisai, Merck KGaA, Solvay, Forest, and Akzo Nobel Wood (ibid.). Their growth is determined by their global strategy, especially in R&D.

Large pharmas and R&D

The increase of R&D in the pharmaceutical sector is considered an industry priority (see European Commission, 2007, "The 2007 EU industrial R&D investment scoreboard"). In a report by the European Commission, pharmaceuticals and biotechnology have overtaken other businesses and have become the top R&D investing sector. On the whole, this sector has shown an increase of 15.9 percent of R&D, or a total of more than US$98732.9 million (or 70523.5 million euros) investment in R&D. The largest increase was 24.3 percent by Merck, followed by AztraZeneca (about 15.5 percent), Roche (about 15.5 percent), Johnson & Johnson (about 12.9 percent), and GlaxoSmithKline (over 10 percent). The pharmaceutical companies that had the largest R&D budget in 2006 are Pfizer, Johnson, GSK, Sanofi-Aventis, Roche, Novartis, Merck, AstraZeneca, Amgen, Bayer, Eli Lilly, Wyeth, Bristol-Myers Squibb, Abbott, and Schering-Plough. Pfizer took the lead in its increase in R&D not just among drug developers but among all industries (see also FierceBiotech, 2007a, "The top 15 R&D Market").

Company profiles in R&D

Pfizer. R&D investment reflects the business strategy pursued by the largest pharmas in the world and they share very similar trends. Pfizer, based in the United States, has a 2006 pipeline budget of $8.34 billion (€5.76B) (Pfizer, 2008c, "Pfizer pipeline – new medicine in development"). In 2007, Pfizer, who lost Torcetrapib in late 2006, causing a laying off 10,000 workers, tried to boost its profile by hiring a new R&D chief for its worldwide operations and has moved its investment in the biotech sector to reduce competition in the generic business. This move is said to threaten the company's profits level (ibid.). A pipeline update by the end of December 2007 shows that the company has 47 Phase II drugs, 11 Phase III drugs including CP-945598 for Obesity; Apixaban for

Venous Thromboembolism prevention; Zithromax/Chloroquine for Malaria; CP-675206 for Melanoma; Axitinib for Thyroid Cancer; Axitinib for Pancreatic Cancer; Sutent for Breast Cancer; Sutent for Colorectal Cancer and Lung Cancer; Maraviroc for HIV in Treatment of Naïve Patients; Lyrica for Epilepsy Monotherapy; Generalized Anxiety Disorder (US); Geodon for Bipolar Relapse Prevention, and 14 biologics in its pipeline. Thirteen projects, including Lasofoxifene for Osteoporosis, Maraviroc for HIV Treatment of experienced patients, and Dalbavancin for Skin and Skin Structure Infections, were abandoned in 2007.

Johnson & Johnson. Based in the United States, Johnson & Johnson is also a leader in R&D with a 2006 pipeline budget of $7.9 billion (€5.40B) (Johnson & Johnson, 2007, "Innovations"). In 2007, despite the controversy surrounding anemia drug safety, Johnson & Johnson had several late-stage drugs that are important to the company's future, these include Telaprevir, two HIV drugs, Golimumab co-developed with Schering-Plough and Rivaroxaban. The mid-term prospect is believed to be promising when 18 to 21 new drugs will be filed or approved over the next three years, five of which are expected by the end of 2007, including Concerta for Adult ADHD, Remicade for Pediatric Ulcerative Colitis and UC colectomy avoidance, Ceftobiprole for Complicated Skin and Skin Structure Infections, Doribax for Nosocomial Pneumonia, and TMC125 for NNRTI HIV/AIDS treatment of experienced patients.

GSK. Following Johnson & Johnson in R&D investment ranking, GlaxoSmithKline, based in the United Kingdom, has a 2006 pipeline budget of $7.51 billion (€5.13B) (GSK, 2008, "Research and development").

GSK is facing short-term challenges, which might effect its stock performance and its competitiveness. This issue was reported to the public when safety concerns were raised about Avandia, a blockbuster diabetes drug and when several big GSK drugs, including Wellbutrin XL, Coreg IR, and Zofran, are facing generic competition. It was noticed that GSK's R&D competitiveness is still in the lead given the fact that it has 33 drugs in Phase III development, which is three times as many as Pfizer (GSK, 2008). In addition, the company will possibly launch as many as 25 new drugs in the next two years and increase marketing of the new drugs of Alli, Cervarix and Tykreb.

GSK's drugs pending approval include Avandia + simvastatin for Type 2 diabetes; Hycamtin for small cell lung cancer and second-line therapy (oral formulation); Globorix for diphtheria, tetanus, pertussis, hepatitis

B, Haemophilus influenzae Type b disease, and Infanrix-IPV/Kinrix for diphtheria, tetanus, pertussis and poliomyelitis prophylaxis; a cure in Pandemic influenza prophylaxis; Gepirone ER for major depressive disorder (once-daily); Lamictal XR for epilepsy; ReQuip XR for Restless legs syndrome; and Trexima for migraine.

Roche. Based in Switzerland, Roche has a 2006 pipeline budget of $5.99 billion (€4.09) (Roche Pharmaceuticals, 2008, "Innovative R&D"). The R&D plan reflects its changing business plans. In 2007, Roche increased its R&D spending and restructured its research work into five arenas of molecular mechanisms: oncology, virology, inflammation, metabolism, and the central nervous system. It has also planned a number of acquisitions. The company's progress in cancer and diabetes research is worth noticing because the company has 33 oncology drugs and five diabetes drugs in clinical trial stage. There are nine additional indications for its blockbuster cancer drug Avastin in Phase III and three more are pending approval. With 40 drugs in Phase III, 32 in Phase II, and 34 in Phase I, the company has a promising position in R&D. For Roche, its drugs pending approval include Xeloda for oral fluoropyrimidine metastatic colorectal cancer (the first line) combo, oral fluoropyrimidine metastatic colorectal cancer (second line) combo; Avastin for renal cell carcinoma, metastatic colorectal cancer (first line) combo oxaliplatin, metastic breast cancer (1st line) combo taxol; and Nicorandil (Sigmart) for acute heart failure.

Novartis. Novartis, a global health stakeholder, has a 2006 pipeline budget of $5.94 billion (€4.06B) (FierceBiotech, 28 November 2007f, "Novartis"). Novartis has experienced success and setbacks in drug development since 2006. In 2007, the FDA approval of Aclasta/Reclastin in the United States and European Union for Aclasta/Reclast is likely to generate $1.2 billion in sales by 2011. The FDA has also approved Tekturna, a potential blockbuster drug for hypertension. Yet safety concerns were raised about the painkiller Prexige, which got a "not approvable" letter. The FDA made a similar decision on the diabetes drug Galvus.

In addition, Novartis continued its niche in vaccines development in 2007, paying Intercell €270 million to license more than ten early and pre-clinical development programs. Also a leader in R&D, Novartis currently has 50 of its 138 projects in Phase II or Phase III. The drugs that anticipate filings in 2008 include QAB149 for COPD; LBH589 for solid tumors; AGO178 for depression; Tifacogin for CAP; MFF258 for

COPD/asthma; RAD001 for solid tumors; Tobramycin for Cystic Fibrosis; and Tekturna for hypertension.

Merck. Based in the United States, Merck had a 2006 pipeline budget of $5.3 billion (€3.62) (FierceBiotech, 28 November 2007e, "Merck – Top 15 R&Ds"). Merck is hoping to gain a potential of a $15 billion market with its cholesterol drug Anacetrapib, a CETP inhibitor, designed to increase good cholesterol and decrease bad cholesterol. Merck's long-term prospects bode well, with several promising drugs. In 2007, Merck received FDA approval of the HIV drug Isentress. The billion-dollar acquisition of Ariad's late-clinical trial cancer drug AP23573 for metastatic sarcomas is said to add ammunition to the company's cancer drug pipelines. Merck's other drugs pending approval are MK-0518 (Raltegravir) for HIV and MK-0517 for chemotherapy-induced nausea and vomiting (approvable). Merck's obesity drug Taranabant, which is in Phase III, expects FDA approval in 2008. This drug could pose a challenge to Sanofi-Aventis's drug Acomplia. Merck has also filed an NDA for Cordaptive (a cholesterol drug that combines a known ingredient with a new one that reduces the risk of flushing).

AstraZeneca. AstraZeneca, based in the United Kingdom, had a 2006 pipeline budget of $4.32 billion (€2.95B), and is taking an aggressive strategy in R&D by spinning off its research institute as a separate company supported by venture capital (FierceBiotech, 28 February 2008a, "AstraZeneca may shake up R&D with spin-off").

Facing serious generic competition to 11 of its drugs (three in the near future and eight in the next eight years), AstraZeneca has aroused concerns from the investment bank Dresdner Kleinwort, which expressed the view that AstraZeneca is likely to be the worst-performing pharma company in upcoming years. This might explain its eagerness to sell off its research institute. A possible source of confidence might be gained from the anticipated approvals of Crestor, an atherosclerosis treatment; Nexium for NSAID GI side-effects – symptom resolution; Nexium for NSAID GI side-effects – ulcer healing; Seroquel for bipolar maintenance; FluMist for Influenza virus; and Symbicort for COPD.

Amgen. Amgen, the world's largest biotechnology company and based in the United States, had a 2006 pipeline budget of $3.73 billion (€2.55) (FierceBiotech, 28 November 2007c, "Amgen – Top 15 R&D"). Amgen has experienced some setbacks and hopes. Safety issues surrounding Amgen's anemia drug, the most profitable for the company, have caused

some concerns about the future of the biotech sector in general. Nevertheless, the company's R&D seems to be moving ahead with several promising drugs, such as Denosumab, a fully-human monoclonal antibody testing for a number of indications, including bone loss induced by hormone, postmenopausal osteoporosis, bone metastases, and prevention of cancer-related bone damage; Cinacalcet HCI for cardiovascular disease in patients with secondary hyperparathyroidism and chronic kidney disease undergoing maintenance dialysis. Other drugs include Panitumumab for first- and second-line colorectal cancer; AMG531, an autoimmune blood disorder drug that treats immune thrombocytopenic purpura, an autoimmune bleeding disorder; and Darbepoetin alfa for cardiovascular disease in patients with chronic kidney disease and Type 2 diabetes.

Bayer. Bayer, based in Germany, had a 2006 pipeline budget of $3.58 billion (€2.45), is planning to expand its biotech sector (FierceBiotech, 28 November 2007c). Since 2007, its plans also consist in aggressively expanding its biotech products, especially in cardiology, hematology, and oncology. Bayer's R&D profile is considered to be in good shape (ibid.). In addition to eight projects submitted for marketing authorization in 2007, Bayer has 14 projects in Phase I, 17 projects in Phase II and 19 projects in Phase III. Promising projects include Rivaroxaban, a potential blockbuster anti-clotting therapy pending for approval by the FDA and European Union, that showed more efficacy than Sanofi-Aventis' Lovenox in a Phase III trial. Other drugs pending for approval include Fosrenol for CKD; rThrombin for bleeding control; Rivaroxaban for VTE prevention; Menostar transdermal for VMS; E2/LNG for HRT (Japan); Magnevist MRA for MRA; Primovist for MRI; Avelon for PID/new indications (EU).

Eli Lilly. Based in the United States, Eli Lilly had a 2006 pipeline budget of $3.47 billion (€2.37B) (FierceBiotech, 28 November 2007d, "Eli Lilly – Top 15 R&D"). Lilly is said to face some challenges to its business growth due to the lack of innovative drugs capable of becoming blockbusters and the upcoming expiration of several of its brands. The company banked on Prasrugel, an anti-clotting drug to treat acute coronary syndrome to take on the blockbuster Plavix. Although Prasugrel has outperformed Plavix in reducing the number of heart attacks and other significant events, it has aroused some safety concerns due to an increasing number of bleeding incidents. Despite Lilly's high hopes, cardiac experts question its efficacy (Martinez and Goldstein, 6 December 2007,

"Big Pharma Faces Grim Prognosis"). Lilly's Phase III drugs include Enzastaurin for non-Hodgkin's lymphoma, Arzoxifene for osteoporosis & prevention of breast cancer, and inhaled insulin. Lilly's revenue is also likely to be affected by the upcoming patent expirations, which could potentially reduce 60 percent of Lilly's revenue.

Wyeth. Based in the United States, Wyeth had 2006 pipeline budget of $3.44 billion (€2.35 billion). Like Amgen and Lilly, Wyeth faced some challenges in 2007 but it also named a new leader to face these challenges. Some of these challenges included that three of its leading drug candidates are delayed in the approval process; the FDA gave a non-approval letter for Bifeprunox, an antipsychotic for the treatment of schizophrenia; HCV-796, a Phase II hepatitis C drug candidate showed adverse events experienced by two patients. Pristiq received an approvable letter from the FDA, but there has been a delay in the launch of this drug for major depressive disorders. The silver lining of these challenges is that Wyeth's development of a new drug for Alzheimer disorder has brought about some hopes for the company. Other drugs also hold some promises, such as the Phase III drugs Lybrel, for continuous contraception; Pristiq for vasomotor symptoms of menopause; and Torisel for renal cell carcinoma III.

Bristol-Myers Squibb. Based in the United States, Bristol-Myers Squibb had a 2006 pipeline budget of $3.39 billion €2.32 (FierceBiotech, 28 November 2008c, "Bristol-Myers Squibb – Top 15 R&D Budgets"). Bristol-Myers Squibb's R&D has shown some promises after heavy investment. Its melanoma drug Ipilimumab, co-developed with Medarex, is expected to be approved; Apixaban, a blood clot therapy, resulting from a $1 billion deal with Pfizer, is expected to become a successor for Coumadin. Bristol-Myers Squibb has also experienced some challenges, however. It is believed that BMS has withdrawn its plan to obtain FDA approval for Vinflunine, which for a while was an important part of BMS's strategy for gastric cancer, transitional cell carcinoma of the urothelial tract, bladder cancer, bladder neoplasms, transitional cell carcinoma, and metastasis. Other drugs that might hold some promise include the Phase III drugs Ixabepilone for breast cancer and metastic breast cancer; Ipilimumab for melanoma; Belatacept for renal transplant, kidney transplantation, chronic kidney failure; Saxagliptin for Type 2 diabetes mellitus, Type 2 diabetes; Apixaban for atrial fibrillation, deep vein thrombosis, pulmonary embolism, atrial flutter, venous thrombosis, and pulmonary embolism.

Abbott. Based in the United States, Abbott had a 2006 pipeline budget of $2.5 billion (€1.71 billion) (FierceBiotech,15 November 2008b, "Abbott – Top 15 R&D Budgets"). In 2007, Abbott planned to follow up on its blockbuster anti-TNF drug Humira by running Phase III trials for additional indications. Although this is a conservative strategy, it ensures some consolidation of its existing market in this area. Several of its compounds are promising. These include Adalimumab (Humira) for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, Ankylosing Spondulitis, juvenile RA, ulcerative colitis, uveitis, giant cell arteritis; Levosimendan for congestive heart failure, acute heart failure, cardiogenic shock, septic shock; ABT-335 androsuvastatin calcium for hypercholesterolemia and dyslipidemia; Atrasentan for cancer and prostatic neoplasms; and Pricalcitol for chronic renal insufficiency.

Schering-Plough. Schering-Plough, based in the United States, had a 2006 pipeline budget of $2.14 billion (€1.65B) and has experienced a turnaround in its R&D progress under the new leadership of Fred Hassan (FierceBiotech, 28 November 2007b, "Schering-Plough – Top 15 R&D Budgets"). Schering-Plough is considered to be one of the most competitive pipelines in the pharmaceutical sector. Its $14.4 billion acquisition of Azko Nobel's Organon made the drug one of the five late-stage drugs in the company's drug repertoire. Other good news includes that its application for Asenapine, a tablet for schizophrenia and bipolar disorder, was approved by the FDA. Despite the expiration of Claritin, Schering-Plough, like other large pharmas, has also tried to preserve its market share of this drug by getting FDA approval for its Claritin/Singulair2 for treating seasonal allergic rhinitis. In addition, Asmanex for asthma and pediatric asthma is pending approval in Japan and in the United States. Also, Nasonex for allergic rhinitis is pending approval in Japan and Noxafil is pending approval in the United States for serious fungal infections.

Overall, R&D spending by the large pharmas does not necessarily translate into innovation. It is noted that although Pfizer invests the most in R&D, it is uncertain of the result of this spending. In contrast, Schering-Plough, for instance, is regarded as having the most promising pipeline despite having the smallest R&D budget among the top 15. It is also important not to underestimate Pfizer's investment in the biotech sector. It is quite possible that this investment might reap rewards when the biotechnology is mature enough to deliver downstream products. This investment might be a long-term strategy rather than a short-term calculation (see related discussions in Martino, 2007, "Comments on top-15 R&D budget").

Large pharmas' profit profile

The large pharmaceutical companies are at the apex of their development history, but they are also facing grave challenges in maintaining their current profit levels. As mentioned in Chapter 1, the pharmaceutical sector is a highly profitable industry (see Dobson, 2001; see also Public Citizen Report, 23 July 2001). In 2006, global spending on prescription drugs had increased, even as growth slowed somewhat in Europe and North America. Sales of prescription medicines worldwide rose 7 percent to $602 billion (IMS Reports, 17 February 2004, "11.5 Percent Dollar Growth in '03 U.S. Prescription Sales"). The leading profit makers remain those who have global presence. The leader in pharmaceutical sales in 2006 was Pfizer with $45,083 million, followed by GSK's $37,034 million; Sanofi-Aventis' $35,638 million; Novartis' $28,880 million; Hoffmann–LaRoache's $26,596 million; AstraZeneca's $25,741 million; Johnson & Johnson's $23,267 million; Merck's $22,636 million; Wyeth's $15,683 million; and Eli Lilly's $14,814 million (Ibid.).

Country-wide, the United States still accounts for most of the sales, about $252 billion in total, an increase of 5.7 percent in 2005 (IMS Reports, 2004). In 2004, the United States comprised about 45 percent of the pharmaceutical market worldwide, while Europe made up about 25 percent. In 2004, US sales grew to $235.4 billion, a growth rate of 8.3 percent compared with an 11.5 percent growth rate in the period from 2002 to 2003 (Trombetta, 1 September 2005). It is worth noting that in a slow-growth economy, US profit growth in this sector remains stable even when other industries have seen slower or no growth (IMS Reports, 2004).

As mentioned earlier, most of the multinationals derive pharmaceutical profits from sales in the markets of developed countries. In addition to Pfizer's cholesterol pill Lipidor, the blood thinner Plavix from Bristol-Myers Squibb and Sanofi-Aventis; the heartburn pill Nexium from AstraZeneca; and Advair, the asthma inhaler from GlaxoSmithKline are among the top-selling drugs (Herper and Kang, 22 March 2006). In 2007, Pfizer's Lipidor remains the top-selling drug of all prescription medicines, followed by AstraZeneca's Nexium. Nexium's sales totaled $5.2 billion (£2.7 billion) and was the world's second-biggest prescription medicine (Pagnamenta, 12 February, 2008).

The growth areas in pharmaceuticals reflect the convergence of several factors. It was noted by Murray Aitken, IMS senior vice-president of Corporate Strategy, that pharmaceutical growth is moving from mature markets to emerging ones and from primary care classes to biotech and specialist-driven therapies. It was also noted that oncology and

autoimmune products have opportunities for growth because they respond to unmet patient needs (IMS, 2007a, "IMS Health Reports Global Pharmaceutical Market Grew 7.0 Percent in 2006, to $643 Billion").

A report by the IMS showed that market and profit trends have reflected population demand and needs, and these trends are likely to continue. Representing largely the industry's viewpoint, the IMS conclusion is based mainly on data gathered from 29,000 data suppliers at 225,000 supplier sites in 100 countries through monitoring 75 percent of prescription drug sales in over 100 countries, and 90 percent of US prescription drug sales, and by tracking more than 1 million products from more than 3000 active drug manufacturers (Gagnon and Lexchin, 3 January 2008). According to this report, most of the 2006 growth, about 62 percent, derives from specialist-driven products, which almost doubled the 35 percent share in 2000 (IMS, 2007). Generics and over-the-counter medicines continue to pose a challenge to a number of primary care classes, including proton pump inhibitors (PPIs), antihistamines, platelet aggregation inhibitors, and antidepressants (ibid.). The growth is slower for these primary care drugs and this might reflect the momentum of generics because of their price competitiveness.

The momentum of generics in 2006 was also confirmed in other reports (such as Visiongain, May 2006). In 2005, world generics sales totaled more than US$45 billion, a 14 percent rate of growth over 2004 (ibid). In 2006, generics continued to be strong and accounted for more than half of the volume of pharmaceutical products sold in seven key world markets, including the United States, Canada, France, Germany, Italy, Spain, and the United Kingdom (IMS, 2007a). This trend is also likely to continue into the next decade (see Visiongain, May 2006). In an estimate by the *Wall Street Journal*, generics sold by top drug makers are likely to exceed $67 billion in annual US sales between 2007 and 2012, as more than three dozen drugs are losing their patents (Martinez and Goldstein, 2007). For example, Pfizer's patent on Lipitor, which ranks as the most successful drug ever invented, expires as early as 2010. Merck will also lose the patents of another three top-selling drugs: Fosamax for osteoporosis, Singulair for asthma, and Cozaar for controlling blood pressure. These three combined represent 44 percent of the company's 2007 revenue. In 2006, Merck had already lost its well-sold Zocor for controlling cholesterol (ibid.).

As mentioned earlier, major global health and demographic issues in the developed and developing countries have contributed to an increasing need for pharmaceuticals but there was an asymmetry in the R&D

of new drugs. For example, in 2006, most of the 31-plus new products launched in key markets were designed to address the health needs of the more affluent populations, such as cancer, cholesterol problems, diabetes, and so on. In this regard, the products that carried most expectation in 2006 were Gardasil®, the first vaccine to prevent cervical cancer; Januvia®, the first-in-class oral for Type II diabetes; and Sutent® for renal cancer (IMS, 2007a).

Of course, R&D drug development that caters to the affluent has paid off in the short term. In particular, drugs designed to contain high cholesterol problems, the top-ranked lipid regulators class, sold particularly well in developed markets and showed an increase of 7.5 percent over the previous year to $35.2 billion, despite patent loss of Simvastatin and Pravastatin in major markets. Other factors that drove up the sales volume include the entries of innovative generics such as Crestor® and Vytorin®, and the increasing demand from Medicare Part D patients in the United States (ibid.).

Given the high incidence of cancer in global populations, it is not surprising to see increasing sales of oncologics on the market (see Ozols, 1 January 2007). Those aimed at specific molecular targets are likely to sell well in the long run. The International Marketing Society (IMS) estimated that oncologics experienced an increase of 20.5 percent, reaching $34.6 billion in 2006 (IMS, 2007a). The sale of oncologics was the highest among the top ten therapeutic classes. Innovation in this class in 2006 resulted in an active program of R&D, leading to the development of 380 compounds. The targeted therapies have revolutionized cancer treatment, changing it from a life-threatening scenario to a chronic treatment-management program. The newer drugs are targeting specific molecules involved with cancerous growth (ibid.).

Other top-selling therapeutics were also designed to respond to population health needs in developed countries. Respiratory drugs sold well (Oversteegen, Rovini and Belsey, September 2007), ranking third among top therapy classes in 2006, and have experienced 10 percent growth in sales to a total of $24.6 billion, as prevalence of respiratory problems, such as allergies or influenzas, is rising. Autoimmune agents also experienced 20 percent growth in 2006 to $10.6 billion in sales. With the sale volume ranking the twelfth among leading classes, growth in autoimmune agents was driven by the increased use of anti-TNF agents such as Remicade® and Humira® and the expansion of approved indications for these products (IMS, 2007a).

Geographically, the share of profits does not necessarily reflect the direction of the growth momentum. On the one hand, North America,

especially the United States, remains the center of action. North America accounted for 45 percent of global pharmaceutical sales, with an increase of 8.3 percent to $290 – a billion higher than the 5.4 percent in 2005. Canada experienced 7.6 percent growth. In comparison, pharmaceutical sales have slowed for three yeas in a row in the five major European markets (France, Germany, Italy, Spain and the United Kingdom), which, experiencing 4.4 percent growth to $123.2 billion, achieved less than 4.8 percent growth in 2005. The growth momentum is clearly with the emerging markets. For example, sales in Latin America grew 12.7 percent to $33.6 billion, while Asia Pacific (outside of Japan) and Africa grew 10.5 percent to $66 billion (ibid.).

On the US market, the increase in consumption is driven by a particular event. Namely, the growth in US prescription drug sales, which grew 8.3 percent to $274.9 billion in 2006, was mainly driven by the Medicare Part D prescription benefit (which extended the coverage to previously uninsured patients and provided more benefits to seniors) (DHHS, 29 September 2006). The plan has increased utilization of generics within new therapy classes, and the availability of new drugs for cancer and diabetes. In 2006, total US dispensed prescription volume grew at a rate of 4.6 percent rate, outpacing the 3.2 percent rate in 2005. It is forecast that US prescription sales growth is likely to remain in the range of 6 percent to 9 percent through 2010, as the Medicare Part D benefit is annualized and there is a need for more cost-effective medicine. It is believed that Medicare Part D has increased retail prescription volume by an estimated 1 to 2 percentage points and pharmaceutical sales by just under 1 percentage point. Clearly, Medicare Part D has directly contributed to strong pharmaceutical sales growth in 2006, as evidenced by the fact that more than 38 million Medicare beneficiaries had some form of prescription drug coverage by June 2006, according to Centers for Medicare & Medicaid Services (CMS) (see DHHS, 2006; IMS, 8 March 2007b, IMS Reports, "US Prescription Sales Jump 8.3 Percent in 2006, to $274.9 Billion").

Several components in the Medicare Part D plan have influenced pharmaceutical sales and will continue to affect the business strategy of the industry (Ibid.). First, the insurers are required to reimburse for all of the brands in six large, highly utilized classes, including antidepressants, antipsychotics, anti-convulsants, anti-retrovirals, anti-neoplastics, and immuno-suppressants. These classes made up about 20 percent of US pharmaceutical sales in 2006 (see the data from IMS, 2007b; and also DHHS, 2006). One related fact is that 17 percent of retail prescriptions in the United States were dispensed through the Medicare Part D

program, and another is the need for savings and cost-effectiveness in Medicare Part D, which increases the demand for generics. The growing demand for generics is inevitable and will directly challenge the industry bottom line. It was noted that 15 of the top 20 products dispensed by Medicare Part D prescription volume were unbranded generic drugs. It was also noted that by the end of 2006, generics utilization, both branded and unbranded, through Medicare Part D already accounted for 63 percent of all dispensed prescriptions (IMS, 2007b). The largest increase was witnessed in generics of lipid regulators, antidepressants, and inhaled nasal steroids. What has contributed to the sharp increase in sales of unbranded generics was the $911 million worth consumption of Teva's Simvastatin, generic Zocor®; $902 million for Apotex's Clopidogrel, generic Plavix®; and $480 million for Greenstone's Sertraline, generic Zoloft®. Generics of Pravachol®, Flonase®, and Mobic®, would also affect the sale when the patents were expired (see the data from IMS, 2007b).

In this scenario of high demands for price cuts, product innovation is the key factor for the growth of the industry. Yet eagerness to roll out new innovations has been dampened by the FDA's cautious approach to approving drugs these days. This attitude is evidenced by the comparatively lower number of approvals in 2005 and 2006.

Nevertheless, this trend does not mean that the golden age of pharmaceutical growth is numbered. New potential lies in the sector's effectiveness in answering to the demands of the global population. As mentioned earlier, this agility in responding to population needs led to a handsome reward in 2005 and 2006, albeit only in developed markets. For example, in 2006, among the approved 18 new molecular entities (NMEs), four therapeutic biologics, and four vaccines, the largest profit potential (with blockbuster status of over $1 billion in global sales) was observed in Merck's ground-breaking cervical cancer vaccine Gardasil®; Merck's Januvia™ (the first of a new class of diabetes treatments); Genentech's Lucentis™ for macular degeneration; Pfizer's Sutent® for renal cell carcinoma; and Celgene's Revlimid® for transfusion-dependent anemia (IMS, 2007b). Merck's ground-breaking cervical cancer vaccine Gardasil® was the real story of pharmaceutical innovation. Similarly, the 2005 best-selling drugs also reflect population health issues. For example, the top-selling products among the 2005 drugs approved by the FDA included Pfizer's Lyrica® for epilepsy/pain; Sepracor's Lunesta® for insomnia; and Amylin/Lilly's Byetta® for diabetes (ibid.).

In 2006, the strongest growth was observed in the biotech sector. The search for new possibilities through biotechnology has led to a robust

20 percent growth to $40.3 billion. New products from this sector include Amgen's Aranesp®, experiencing a 42 percent increase and reaching $3.9 billion; Amgen's Enbrel® with a 12 percent increase to $3.1 billion; and Amgen's Neulasta® with a 28 percent increase to $2.9 billion. Oncologics showing strong growth are Rituxan® with an 18 percent increase to $2.1 billion; Avastin® with a 79 percent increase to $1.7 billion; and Herceptin® with an increase of 66 percent to $1.2 billion (facts cited from IMS, 2007b).

The unlimited possibilities in the biotech sector provide some hope for innovative pharmaceutical ideas. The approval of Sandoz's Omnitrope, a human growth hormone, by the US Food and Drug Administration in May 2006, through existing 505(b)2 pathway, was widely seen by the industry as a landmark decision for biotech products. Despite the uncertain prospects of the biotech sector as a whole, this development bodes well for other drugs in the pipelines because of the low barriers of entry and lack of regulation in this sector (see related discussions in IMS, 2007b). This explains why the industry has boosted its investment in the biotech sector. It was estimated that since 2005, large pharmas have spent $76 billion in buying up biotech firms (Mantone, 6 December 2007, "Big Pharma's Bitter Pill").

Despite the high hopes for biotech, it is questionable if it is the magic bullet that could possibly resolve all the problems facing the industry. The long-term outlook of the industry remains highly volatile. As IMS has pointed out, the pharmaceutical sector is likely to continue growing globally, but growth in developed societies will remain slow, with the United States leading at a growth rate of 6 percent to 9 percent through 2010 because of possible changes in the health care system after the 2008 presidential election. In addition, the expiration of some brands in 2006, estimated to be worth $14 billion of sales, and other brands' sales, worth $12 billion in 2007, in lipid regulators, antidepressants, platelet aggregation inhibitors, anti-emetics, and respiratory agents are expected to have had some impact on the industry.

Given the imbalance in supply and demand/need, the industry will be under increasing pressure from the outside to change its operation strategy.

Outsiders' perception of the pharmaceutical sector

In any discussion of the challenges facing the industry, it is important to address what outsiders perceive as the major strategy taken by the industry to maintain a robust growth level these days. These issues were

summarized in a number of publications but the most comprehensive summary was offered by the former editor of the *New England Journal of Medicine*, Marcia Angell, in her 2004 book *The Truth about the Drug Companies*. Her criticism summarizes the concerns of the public about the growth strategy employed by the industry, that is, the failure to strike a balance between a high profits goal and its public heath obligations.

Problems with the cost of innovation

It is widely agreed that the pharmaceutical industry requires a high level of innovativeness and that the industry's efforts in generating certain innovative drugs has been quite successful in the 1990s. Yet increasingly, questions are raised as to who has really contributed to the innovativeness. It was pointed out that some of the basic research leading to eventual drug development has been carried out by universities and research institutions (see SciDeve, 2008; see also Wikipedia, 2007b; Angell, 2004). Angell pointed out that one-third of drugs marketed by the major pharmaceutical companies were licensed from universities or small biotech companies and these drugs were believed to be the most innovative ones (Angell, 2004; see also Lamberti, 2001). Some of the most innovative and effective drugs, such as Taxol, Epogen, and Gleevec, derived from NIH-funded or university research.

In the case of the discovery of AZT, an HIV treatment, it is believed that the scientist Samuel Broder, head of the National Cancer Institute in the United States, and his colleagues at the Duke University, had more to do with the discovery of the AIDS drug AZT than Burroughs Wellcome, the company that actually patented it.

Some questioned the innovativeness of the pharmaceutical sector because of the abundance of the "me-too" drugs on the market. It was pointed out that a large amount of resources were devoted to the development of a few drugs and that this redundancy could jeopardize the industry's ability to innovate. Angell reported that by 2004, there were six statins (Mevacor, Lipitor, Zocor, Pravachol, Lescol, and Crestor) on the market as lipid regulators and they are variants of Mevacor. In addition, it was noted that only 17 of the 78 drugs approved by the FDA in 2002 were regarded by the FDA as improvements over older drugs, with the rest being no more effective than the old ones. In another account, between 1998 and 2002, only 133 of 415 drugs approved, or 32 percent of the total, were new molecule drugs and only 14 percent were considered to be "truly innovative" (Angell, 2004). And, only 3 of the 7 innovative drugs approved in 2002 came from PhRMA members (ibid., 2004).

Critics of the pharmaceutical industry also voice their concern about the need to sustain a high level of innovation through pursuing a high-cost strategy. The cost of developing a drug is highly controversial and so far there is little knowledge about what the true cost is (see Public Citizen, 2001; Cptech, 2001, "Pharmaceutical industry R&D costs: Key findings about the Public Citizen Report"). One estimate in 2000 showed that the cost was no greater than $175 million after tax but another estimate by Public Citizen (2000) showed that the actual after-tax cost of developing a drug was less than $100 million (Angell, 2004). The $802 million estimated by the Tufts' Center was deemed by the industry's critics to be high, believing that this figure might be a pre-tax estimate that included the opportunity cost. Yet the industry counter-argued that this figure did not include the opportunity cost of capital and that in any case, including this opportunity cost is a usual practice in financing. The critics also pointed out that tax credits for the pharmaceutical companies could be as high as 50 percent when the tested drugs are orphan drugs, such as in the case of Retrovir, an AIDS drug (Angell, 2004). It was also pointed out that the tax rate for Pharmas was much lower between 1993 and 1996, 16.2 percent, compared to 27.3 percent for other major industries (see Public Citizen, 2001). The critics believed that if we took into account all the tax incentives that the industry has received, the actual after-tax estimate of the $802 million could be as low as $266 million (Angell, 2004).

In addition, when observing the phenomenon that a large amount of spending on R&D has produced few innovative drugs, the critics have also raised the issues of efficiency and effectiveness of pharmaceutical development (Angell, 2004), the latter of which has a direct impact on population health.

Effectiveness, validity and reliability

So far, the industry's efforts to generate effective cures for diseases, especially those in the developed societies, is a known achievement. Drugs like Prozac, Gleevec, statins, Viagra, Epogen, Taxol, and Prilosec are direct evidence of this effort. But questions were raised about the effectiveness of some heavily promoted drugs. It was pointed out that an NIH sponsored experiment, ALLHAT (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), involving 42,000 people and 600 clinics, which was also the largest experiment of this kind, showed that a generic diuretic pill, the least expensive of all the four drugs used in the experiment, was as effective as the other three drugs, Cardura by Pfizer, Zestril by AstraZeneca, and Prinivil by Merck.

The inexpensive old generic drug was also said to be better at preventing some of the complications of high blood pressure, especially heart disease and strokes (Angell, 2004). In another NIH study on prevention of adult-onset diabetes, it was found that diet and exercise was more effective than using a placebo or the drug metformin, the generic form of BMS's Glucophage). When examining these studies, the critics raised the same issue about the efficacy claims that had been made by the pharmaceutical industry.

In general, the critics raised issues concerning the industry's claims about pharmaceutical effectiveness in several areas. First, they point out that the potential of some new drugs tends to be overestimated, such as in the case l'Exubera, an insulin inhaler (*Le Monde*, 19 October 2007). The critics also questioned the practice of comparing a new drug with the placebo instead of comparing the new drug with an older drug when evaluating the effectiveness of the "me-too" drugs in clinical evaluations. There were also some concerns about the "make-believe" phenomenon, as evidenced by a number of cases or incidents (Angell, 2004). A survey showed that industry-sponsored research was nearly four times more likely to be favorable to the company's product as NIH-sponsored research (Bekelman, et al., 2006). In addition, the critics also said that negative results seemed to be suppressed (Angell, 2004). In another case, it was pointed out that Parke-Davis tried to promote Neurontin, an epilepsy drug, for off-label uses for other conditions by asking academics to endorse company-sponsored articles, or use medical liaisons to disseminate the article widely to practicing doctors (ibid.). These promotion efforts were believed to have led to Neurontin becoming a blockbuster with $2.7 billion sales in 2003 (ibid.).

The other example cited by the critics was the practice of using Phase IV surveillance studies to raise the drug's publicity and to influence doctors' drug choices and formulary recommendations, instead of improving drug effectiveness (Angell, 2004). It was also pointed out that some Phase IV studies were not published (Privitera, 2003). Phase IV are often contracted by CROs, using networks of private doctors in their offices and as a result, doctors are likely to prescribe the medicine tested (Angell, 2004). As a prominent example, Angell pointed out that the recommended use of estrogen and progesterone hormone replacement therapy to prevent heart disease was mainly based on industry-sponsored research and that this conclusion supporting the use of hormone replacement therapy has been refuted by NIH-sponsored research since the mid-2000s. New research has questioned the effectiveness of hormone replacement therapy in preventing heart disease in

menopausal women. For example, the Women's Health Initiative (WHI) Hormone Program, jointly sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), part of the National Institute of Health, found that this therapy increased the risks of breast cancer, heart disease, stroke, blood clots, and urinary incontinence (National Cancer Institute, 2007).

The point of contention was that instead of initiating innovative research, the industry tried to resort to business strategies to promote the efficacy claims of the new drugs. The critics believed that these strategies do not necessarily reflect the scientific validity or reliability of the new drugs in curing diseases (Goozner, 2004). The critics even questioned the pharmaceutical companies' contributions to the drug development process, or the clinical evaluations of a drug. The critics believed that the industry included that process as making up the entity of "innovativeness" (Angell, 2004). It was believed that this contribution to clinical evaluation is often used as the key evidence supporting the pharmaceutical companies' claim of the need to maintain a "high-price" scenario for drugs. Furthermore, the critics argued that even that claim was questionable because these days, the clinical trials were arranged through contract research organizations (CROs), which conducted about 80,000 clinical trials in the United States in 2001 and included 2.3 million human subjects (ibid.). It is the CROs that are responsible for conducting clinical trial evaluation of new drugs.

The question of maintaining the high profit scenario

The questions surrounding the "high-profit" scenario have tarnished the image of the large pharmaceutical companies. As mentioned in Chapter 1, the profits of pharmaceutical companies rank as one of the highest, with the average net return as a percentage of sales at more than 17 percent, higher than most other industries. Angell pointed out that in 2002, the total profits of $35.9 billion for the ten drug companies in the Fortune 500 were more than those for all the other 490 businesses combined of $33.7 billion (Angell, 2004; see also Newton, Thorpe and Otter, 2004).

Critics have raised more issues with the pharmas' strategies to maintain the "high-profit" scenario than just the high-profit scenario itself (see Angell, 2004). They believed that the pharmas have generated very creative strategies to maintain the profit at a high level. To begin with, it was noted that unlike most commodity prices, which charge the customers on the basis of manufacturing cost and market-driven profit margins, the prices of drugs are determined by what the pharmas

perceive as the monetary value of the drugs, especially in the United States. In addition, Angell (2004) argued that drug prices in the United States reflected what the patients were willing to pay, not the R&D cost or the medical value of the medicine. Her argument implied that the prices would be much lower if they were based on the calculation of the R&D and manufacturing costs because the public sector has paid for some of the most innovative drugs, such as Taxol, Epogen, Procrit, and Neupogen. For example, in the case of Taxol, $10,000 to $20,000 was charged for a year's supply of Taxol when it first came on the market. This price was believed to be a 20-times' markup (ibid.). Another case was that of Claritin, Schering-Plough's top-selling drug. The price of Claritin was raised 13 times over five years, to a total increase of 50 percent, which was believed to have outpaced the rate of general inflation (ibid.).

The most mentioned practice to maintain the "high profit" scenario was the extension of the patent life of a drug (Goozner, 2004). The pharmas' efforts to extend patents was noted by their critics in a number of strategies. For example, the Hatch-Waxman Act provided up to five years of additional patent life for drugs experiencing long delays in coming to market because of clinical testing and approval (Angell, 2004). In addition, if a brand-name company sues a generic company for patent infringement, FDA approval of the generic drug would automatically be delayed for 30 months. Also, the company can extend the patent life of a brand by suing a generic company who intends to make copies of the brand that has just expired.

This strategy of extending patents through legal maneuvers is believed to have been widely practiced by pharmaceutical companies. It was noted that since the passing of Hatch-Waxman, the brand name companies routinely file not just one patent on their blockbusters, but a series of them that spreads through the life of the first one. The companies list any patents they want and use the legal option to get 30 months' extension. Another patent privilege was added when the Food and Drug Administration Modernization Act of 1997 allowed six months of extension of patent life if the drug is tested on children. It was noted that AstraZeneca has taken advantage of these rules and extended the patent life of Prilosec (Angell, 2004). Scherling-Plough has used similar tactics to extend the exclusive rights of Claritin and the same is true for Lilly's Prozac, and GSK's Paxil (ibid.).

Alternatively, the companies can use other strategies than litigation. For example, the owner of the branded drug will try to carve out a share in the generic market by introducing a generic version before the patent

expires (Wikipedia, 2007b). Also, the company can introduce a "me-too" drug before a top-selling brand drug expires. This practice was noticed in the rolling out of the new heartburn drug Nexium to extend the life of Prilosec, which was a top-selling drug that grossed $6 billion in global sales for AstraZeneca; the campaign to market the replacement was believed to have cost half a billion US dollars (data cited from Angell, 2004). A similar practice was observed in the promotion of Clarinex over Claritin, which accounted for $2.7 billion of one-third of Shering-Plough's revenues (data cited ibid.). There is also the new "me-too" of Levitra and Cialis to compete with Viagra (data cited ibid.).

This need to maintain high profit through extending the market life of a blockbuster has created a competition among "me-too" drugs, such as in those lipid regulators. It was believed that Merck's Zocor, Pfizer's Lipitor, BMS's Pravachol, Novartis's Lescol, and AstraZeneca's Crestor were all variants of Merck's original's Mevacor (Angell, 2004). Similarly, GSK's Paxil and Pfizer's Zoloft are competitors of Lilly's Prozac, which accounted for 25 percent of Lilly's revenues before its patent expiration (data cited from Angell, 2004). Lilly then re-branded Prozac by naming it Prozac Sarafem for treating premenstrual dysphoric disorder (ibid.). The "me-too" drugs focus on high profitability and therefore they target certain conditions, such as: (1) chronic conditions affecting a larger number of people; (2) customers who can afford to pay; and (3) a highly elastic market (such as drugs for hypertension or cholesterol issues). In order to maintain the profit momentum of the first blockbuster, the industry has neither reduced the prices of the "me-too" drugs" nor expanded choices (ibid.).

According to the critics, another strategy to maintain the "high profit" scenario is to promote diseases over health. Or in Angell's (2004) words, the pharmaceutical companies "promote diseases to fit their drugs," instead of promoting cures for diseases. Some call this phenomenon "disease mongering" or overmedicalization (Moynihan and Cassels, 2005; PLOS Medicine, 2006, *A Collection of Articles on Disease Mongering*).

Critics of the industry also observed that overmedicalization has become a phenomenon in developed as well as prosperous developing societies, such as Taiwan, or the urban populations in China. In the United States, it was noted that in 1965 when Medicare was enacted, drugs were cheaper and Americans took much fewer prescription drugs (Angell, 2004).

Aggressive marketing

Related to the increasing consumption of pharmaceuticals in developed societies, especially in the United States, is the creative marketing efforts

of the industry and this is also the major criticism directed against the industry. Critics argued that most pharmaceutical expenditure has been invested in boosting marketing, not on innovative R&D (see, for example, Angell, 2004).

Estimates of the marketing budget of large pharmas vary. A conservative estimate showed that about US$19 billion a year was spent on the promotion of drugs (Moynihan, 2003b, "Who pays for the pizza? Redefining the relationships between doctors and drug companie"). But Angell (2004) pointed out that the estimate should be higher and that the budget for marketing and administration actually is larger than that for R&D and the marketing expenditure has continued rising. For example, in 1990, R&D was 11 percent of total sales; 14 percent in 2000; 35 percent in 2001; and then about 15.9 percent in 2006. In comparison, it was suggested the marketing budget has been constantly higher (ibid.). For example, the marketing budget was estimated to be 36 percent of the sales revenue in 1990 (ibid.). In 2002, which was the focal point of Angell's analysis, an estimate showed that the pharmaceutical companies had sales totaling $217 billion with a profit margin of 17 percent, but they only spent 14 percent on R&D. In contrast, about 31 percent was spent on marketing and administration.

The venues for marketing drugs are several and in exception to the ill-regulated regions in developing countries, the United States is one of the most liberal systems in allowing pharmas access to various marketing channels. These channels include health care journals, direct advertising to the general public, physicians, other health care providers, legislators, and health events (such as professional conferences and continuing education).

Among all the targets, marketing to physicians has one of the most important impacts because physicians are on the front line of contact with patients. They are the primary decision makers for prescription drugs use. They make decisions not only for FDA-approved drug use but also for the off-label use. They are the key to boosting prescription drug sales. Often, the physicians' offices are where the field troops, the pharmaceutical sales people, are deployed (see Myers, 2007). Pharmaceutical sales personnel compose the core of the aggressive marketing effort and their size is by no means modest for any pharmaceutical company. It is believed that a medium-sized pharmaceutical company might have a sales force of 1000 representatives and the number can exceed tens of thousands of sales representatives for the largest companies. It was noted that by 2003, there were approximately 100,000 pharmaceutical sales reps in the United States interacting with more

than 120,000 pharmaceutical prescribers (see Robinson, November 2003). It was also noted that these had doubled in the four years from 1999 to 2003, costing more than $5 billion on communication with physicians, and this statistic was believed to be a conservative estimate. One of the tools used by pharmaceutical companies to market drugs to physicians and health providers is the use of specialized health care marketing research companies to perform marketing research. One of the marketing tools is free drug samples. Angell (2004) reported that in 2001, drug companies sent 88,000 representatives to give doctors nearly $1 billion worth of "free samples."

In addition to physicians, the other marketing target are the third-party payers, such as private insurance or public health bodies (e.g., the NHS in the United Kingdom, Medicare in the United States), who decide which drugs to pay for, and restrict the drugs that can be prescribed through the use of formularies. The buying power of the third-party can be very large because they restrict the brands, types, and number of drugs that they will cover. Angell reported that large pharmas in the United States derived a large part of their revenues from employee-sponsored insurance and state-run Medicaid programs (Angell, 2004). Not only can the third party payers affect drug sales by including or excluding a particular drug from a formulary, they can affect sales by tiering or placing bureaucratic hurdles to prescribing certain drugs as well. The state Medicaid programs often try to save programs by asking for deep discounts for drugs. This is also true for the new Medicare Part D prescription plan in the United States.

The most controversial channel of marketing is direct-to-consumer (DTC) advertising. As mentioned earlier, liberation in the presentation of risks in advertisements of drugs in the 1997 legislation allows direct marketing of prescription drugs to consumers. It was noted that expenditures on DTC ads almost tripled between 1997 and 2001, increasing from 25 percent to 64 percent in total TV ads. It was pointed out that in 2001, the FDA had only 30 reviewers to review 34,000 DTC ads (Angell, 2004). The critics believed that DTC ads mislead consumers, making consumers pressure doctors to prescribe new, expensive, and often marginally helpful drugs, even when a more conservative option might be better and safer (see also US Department of Health and Human Services, August 1999, "FDA Guidance for Industry on Consumer-Directed Broadcast Advertisements").

The center of the controversy related to pharmaceutical marketing is not the size of the marketing budget or force, but the methods employed (see the results of a 2005 review by a special committee of the UK

government in the EU context; European Public Health Alliance, 2008). Criticism in this area surrounds accusations and findings of influence on doctors and other health professionals with inappropriate methods; buying research support; biased information to health professionals (see No Free Lunch (2008); see also Kaufman, 6 May 2005); high-prevalence advertising in journals and conferences; political influence peddling (more than any other industry in the United States (Ismail, 7 July 2005); sponsorship of medical schools or nurse training; involvement in continuing educational events and playing a role in influencing the curriculum (Moynihan, 2003a).

Key evidence was illustrated in several cases with the role of sales reps in influencing physicians often being criticized. For example, drug reps give doctors free samples, educational grants, consulting fees, free attendance at medical conferences in resorts, lavish gifts, expensive dinners, vacations, junkets to luxurious settings, or cash rewards, which are actually frowned upon by the American Medical Association and compromise the ethical guidelines of the PhRMA (Angell, 2004). Another way to influence physicians is through health meetings. It was noted that the number of promotional meetings has increased dramatically from 120,000 in 1998 to 371,000 in 2004 (Hensley and Martinez, 15 July 2005). In 2000, the top ten pharmaceutical companies were spending just under US$1.9 billion on 314,000 such events (Quintiles Transnational, 2001; see also Gagnon and Lexchin, 2008). Some of these meetings are framed as continuing education events. For example, in 2001, drug companies paid over 60 percent of the costs of continuing medical education and contracted private medical education and communication companies (MECCs) to plan the meetings, prepare teaching materials, and produce speakers (Angell, 2004). MECCs often have some links, or are even owned by large advertising agencies (ibid.). They are the go-between for the drug companies and doctors to promote drugs.

Influence peddling

The leading controversy is what many perceive as political influence peddling (see The Center for Public Integrity, 2005).

First, the pharmaceutical and health products industry is the largest among all industries. For example, in 2005, the sector spent more than $675 million in federal lobbying in the United States (Center for Public Integrity, 2005). It was noted that the industry hired around 3000 lobbyists, more than a third of whom were former federal officials in the House, the Senate, the FDA, the Department of Health and Human

Services, and other executive branch offices. These lobbyists for the industry had worked for the Ways and Means Committee, Senate Judiciary Committee, Health, Education, Labor and Pensions Committees. According to Public Citizen, from 1997 to 2002, the industry spent "$478 million on lobbying" and the planned budget of lobbying seems to have increased from year to year (Angell, 2004, p. 198). Second, political influence peddling is carried out through generous campaign contributions. For example, in 1999–2000, drug companies gave 20 million in direct campaign contributions, 80 percent of which went to the Republicans, and another $65 million in "soft" money (ibid.). Third, according to Angell (2004), influence is practiced through the setup of "front groups" masquerading as grassroots organizations, such as Citizens for Better Medicare, which spent $65 million in 1999–2000 to fight against any form of drug price regulation. United Seniors Association, spending $18 million in the 2002 election, supported PhRMA's position. Fourth, critics said that the large pharmas had tried to influence the FDA. For example, the PDUFA (Prescription Drug User Fee Act) passed in 1992 allowed the FDA to charge the large pharmas user fees for drug evaluations, which had accounted for more than half of the FDA's budget with a total of more than $260 million in 2002 (ibid.). This presented an obvious conflict of interest issue. Under this act, the FDA, who takes money from the pharmas, is under legal mandates to approve drugs faster in the United States than in their counterparts in Europe. In one case, the FDA hearing records that "at 92 percent of the meetings at least one member had a financial conflict of interest," and "at 55 percent of meetings, half or more of the FDA advisers had conflicts of interest" (Cauchon, D. 25 September, 2000, "FDA advisors tied to industry"; Gribbin, 18 June 2001). These political endeavors were said to have contributed to some form of political favoritism (Goozner, 2004; Angell, 2004).

Inadequacy in meeting the needs of developing countries

A more global criticism of the pharmas is the ignoring of its social and humanitarian responsibilities in the global community. This criticism originates from the late 1990s, during the height of the AIDS epidemic. In 2003, South Africa's Competition Committee ruled that GSK and Boehringer Ingelheim had violated the country's Competition Act by charging high prices and refusing to license their patents for generics manufacturers in return for reasonable royalties (BBC, 10 December 2003, "AIDS activists say GlaxoSmithKline is to allow the manufacture of cheap generic drug versions in South Africa"). Under the pressure

from human rights activists, both companies had to agree to grant licenses for generic production of anti-retroviral drugs. Yet initially, the large pharmas had threatened to sue the South African government. In return, the Clinton Administration, who represented the pharmaceutical interests, threatened trade sanctions. If it was not for the vocal support from civil society, the pharmas would have prevailed in their insistence on not providing life-saving medicines at a lower price. Today, despite the DOHA declaration and 30 August decision allowing compulsory licensing and parallel imports for resolving some public health challenges, poor countries still face major difficulties in invoking these measures for pharmaceutical access. And the critics see that the major hurdle comes from the immense influence of the pharmas on global health care politics.

Challenges facing the multinational pharmaceutical industry

The major challenges facing the multinational pharmaceutical companies are several. Some of the most mentioned challenges include innovation, increasing competition from generics, asymmetry in addressing population health needs and over-concentration in developed markets, quality control, and pressure from regulatory authorities for price control. Among all the challenges, the need for innovative R&D is widely regarded as the most formidable challenge facing the industry, but innovation also has a two-way interaction with other challenges. Innovation requires an astute understanding of population health issues, etiology, environment, social determinants, cultural practices, and genetic origins. In other words, it is a test of the imagination in finding the widest range of possibilities of solutions. When the pharmaceutical makers have innovative R&D, which assures an inexhaustible supply of effective pipelines, then other challenges will be minimized. Even critics of the industry praise the pharmaceutical industry for what it has accomplished since the nineteenth century. The invention of antibiotics, aspirin, penicillin, statins, and so on has significantly improved the population health, both in quantitative and qualitative terms. As Angell (2004), one of the most candid critics of the industry, bluntly put it, "the truth is that good drugs sell." Gleevec provided the most relevant case in point; Angell (2004) commented that Gleevec can sell itself even without a major marketing and promotional effort with information from credible professional journals and meetings. The same can be said about Lipitor and Zoloft.

The need for innovation has never been more urgent given the difficulty in finding truly new drugs, increasing scrutiny from regulatory authorities, and the imminent expiry of patents on major profitable drugs. It was noted that between 2002 and 2006, the industry brought 43 percent fewer new chemical-based drugs to market than in the last five years of the 1990s, despite their doubling of research and development spending (Centre of Public Integrity, 2005). The situation is even more troubling when considering the scenario in which the pharmas are losing patents for their high-profit drugs, as mentioned earlier. According to one estimate, it is predicted that $40 billion in US sales could be lost at the top ten pharma companies because of patent expiration of 19 blockbuster drugs by 2008 (Ebisch, 2005).

The issue of innovation has become problematic for the pharmas since the beginning of the 2000s. It was forecast between 2000 and 2004, only 32 of 314 drugs would be truly innovative: these drugs coming mainly from Pharmacia, Merck, BJS in 2000; Merck in 2001; none in 2002; and one each from Pharmacia, Wyeth, and Abbott in 2003, with the conspicuous absence of either Lilly or Schering-Plough (data from Angell, 2004). In one instance, in the third quarter of 2007, Novartis's profit return was below the estimate of analysis because of its loss of three patents of Zelnorm (colon problems), Lotrel (hypertension), and Lamisil (ringworm) (*Le Monde*, 2007). Similarly, in 2006, the loss of patent life by two of the most successful and largest brands – Zoloft and Zocor – has impacted the profit profiles of the pharmaceutical makers (IMS, 2007b). A similar negative consequence is likely to follow with the expiration of Norvasc® and Ambien® (ibid.).

It is predicted that 150 mid-sized new compounds will be needed by 2008 in the US alone to compensate for the profit gap (Ebisch, 2005). The pharmaceutical companies have no other option but to increase their investment in R&D. In this case, innovation is not a choice, but a survival requirement. A counter strategy has been suggested that while pharmaceutical companies today focus on blockbusters, in seven years' time they will have to focus on thousands of drugs to maintain their profit levels (ibid.).

Some also suggest that one way to get out of this dilemma is to use biotechnology to improve innovation, but the concern with biotechnology in drug development lies in its high cost and high uncertainty (see, for example, some related discussions in Griffiths, 2004). The large pharmas' alliance with the biotechnology sector has certainly widened possibilities for innovative new drugs, as biotechnology makes it possible to manipulate cells' genetic structure to produce specific proteins.

The biotech sector complements the large pharmas' expertise. The new knowledge gained in molecular biology in the 1970s allows a new method of synthesizing potential drugs that is not in the traditional pharmas' expertise. This alliance allows the large pharmas to benefit from the fruit of the R&D, while the small biotech companies gain financing, marketing, and management support from the large pharmas (Schweitzer, 1997). Some fruitful results have been observed in the development of biogenerics and many companies focus on erythropoeitin because of the size of the market (see Griffiths, 2004). Yet overall, the future of biotech gaining a dominant position remains more a calculation than a reality.

Besides the uncertainty in biotechnology, some saw the competition from generics as a challenge to the pharmas (see Martinez and Goldstein, 2007; see also IMS, 2007). The impetus for the growth of generics derived from the Hatch-Waxman Act legislation in 1984, which helped increase the generics' share from 20 percent of prescriptions in 1984 to 50 percent in 2002 (Angell, 2004). As mentioned earlier, the patent expiration of some major drugs, which started in the early 2000s, provides another impetus. This trend, beginning with the expiration of Lilly's Prozac and AstraZeneca's Prilosec for heartburn and amounting to $6 billion in 2001 for those companies, was believed to have an impact on the revenues of $35 billion in annual loss for large pharmas (ibid.). This trend continued when Bristol-Myers-Squibb's lost its most profitable drug Glucophage for diabetes, and Schering-Plough lost Claritin in 2002, the latter of which accounted for one-third of the company's revenues (ibid.).

The increasing momentum of the demand for generics added another impetus for the growth of generics. It was noted that the profits of such large pharmas as Pfizer (United States) and Novartis (Switzerland) were already affected by the increasing sale of generics (*Le Monde*, 2007). In 2007, Pfizer announced that its profits in the third quarter, US$761 million, were much lower than the profits in the third quarter of the previous year of about US$2.8 billion. In this trend, the emergence of so-called "branded generics," which are priced between the brands and generics, could pose another challenge to the makers of brand drugs (related discussions from Angell, 2004).

Asymmetry in meeting population health needs

The major challenge to innovation is related to the asymmetry in producing effective drugs in global settings. As mentioned in Chapter 1, most of the drugs have been produced to meet the demand and needs

of the populations in developed societies, especially drugs for such chronic illnesses as cardiovascular problems, hypertension, diabetes, obesity, and so on. There has been very little investment in producing cures for those diseases or illnesses facing developing countries. Some global attention to neglected diseases, such as malaria, TB, onchocerciasis, and trachoma, in resource-poor countries is a fairly recent phenomenon. The controversy surrounding the patents of AIDS drugs has revealed the extent of this asymmetry in drug development to meet global health needs. As mentioned in Chapter 1, the focal point of the criticism against the global pharmas was that most of the disease burden has been in developing countries, but more than 90 percent of the cures were made for the populations in developed societies. The criticism was not just about the high-profit or patent protection scenarios for the large pharmas, but was also about the lack of understanding of this asymmetry, which actually helped the spread of diseases and epidemics. The litigation against South Africa by 41 pharmaceutical companies in March of 2001 for South Africa's enacting the country's Medicines Act, which would allow compulsory licensing and parallel imports of cheap AIDS drugs, was a reality check for the world and pharmaceutical industries. This makes plain to the world that the unfortunate dilemma faced by drug making is about striking a balance between business reality and population health reality.

The worry about price control

Price control, a major challenge facing the industry, occurs as a result of failure to address such other challenges as population health needs and over-concentration in the markets in developed societies, along with short-sighted strategies to protect market share and inadequacy in innovativeness.

The possibility of price control in the United States is said to be a major concern for large pharmas because, as mentioned in Chapter 1, more than 45 percent of their profits derive from pharmaceutical sales there. Yet the United States is also the only country without pharmaceutical pricing regulation that allows the pharmas to set pharmaceutical prices. As mentioned in Chapter 1, other major industrialized countries or emerging powers, such a Australia, Canada, and most EU members (such as France, Germany, Italy, Japan, the Netherlands, Spain, Switzerland, and Sweden) have some form of price control. Most countries, such as Canada, use reference indicators, such as the median prices of the pharmaceuticals in other developed countries. The United Kingdom does not regulate the price, but puts a ceiling on the profits.

The concern for pharmaceutical prices in the United States is not unfounded. First, the US population is graying. Second, the prevalence of chronic health issues, such as hypertension, diabetes, cardiovascular problems, depression, and respiratory problems has increased demands for effective cures. It was noted that from 1960 to 1980, the sale of prescription drugs as a percentage of GDP in the United States was stable, but from 1980 to 2000 this figure had tripled. In 2002, the total was more than $200 billion a year, which includes consumer purchases at drug stores and mail order pharmacies and 25 percent markup for wholesalers, pharmacists, and other middlemen, and retailers (Angell, 2004; see also Center for Policy Alternatives, 2000, "Playing fair: State action to lower prescription drug prices"). In total, this figure accounted for about 50 percent of the global sales of $400 billion (Angell, 2004).

Price concern is most acute among the elderly in the United States as life expectancies have continued to increase (Long, 1994; see also Lichtenberg, 11, July 2007, "Yes, new drugs save lives"). Between 1991 and 2004 alone, US life expectancy increased by 2.33 years and as this trend continues, the need for prescriptions has also increased (ibid.). In 2003, it was pointed out, the average price of the 50 drugs most used by senior citizens was nearly $1500 for a year's supply and it was noted that in this scenario, an American who does not have any health coverage would have to spend $9000 from their own pockets per year (Angell, 2004). A report pointed out that an estimated one million Americans bought their medicines from Canadian drugstores in 2002, totaling a $700 million business, or over the Internet, despite the US Congress' legal ban (see Barry, April, 2003). In 2002, there were 140 Internet pharmacies in Canada, an increase from 10 percent in 1999. And the cross-border drug trade is believed to be growing. It would be no exaggeration to say that Canada is likely to become America's backdoor pharmacy if the drug prices continue to grow at their current pace.

In the United States, there are increasing demands from the public for legislation to enact some forms of drug price control through the requirement of cost-effectiveness and use of generics alternatives. This is said to have put new pressures on pharmaceutical manufacturers to consider those issues related to value, pharmaceutical pricing, and affordability (see related discussions in IMS, 2007b). This has also given rise to the "MacDonaldization" of pharmaceutical provision in the United States, exemplified by the affordable pharmaceutical plans offered by one of the largest retail pharmacies, Wal Mart.

In addition to private initiatives, the US government has also taken notice of the need for affordable pharmaceuticals. Against the

background of an increasing demand for affordable medicine, the Medicare Part D Plan emerged. This plan had made certain promises to address the pharmaceutical price issues facing the American elderly.

The Medicare prescription drug benefit, or Medicare Part D Plan, passed by Congress and signed into law by the President, made several promises. First, on savings, it promised to save seniors an average of $1200 a year (US Department of Health and Human Services, 2006). In addition, it also promised savings on premiums, because the premiums for these plans will even be lower than the ones the seniors signed up to in 2007, and this lower rate is likely to benefit 83 percent of beneficiaries as some plans would have premiums of less than $20 a month. The other promise is the increase of choices and expansion of coverage. Beneficiaries are promised that they will have more plan options that offer enhanced coverage, including zero deductibles and coverage in the gap for both generics and preferred brand name drugs. Some plans have promised to increase the drugs on their formularies by 13 percent (Department of Health and Human Services, 2006).

In a sense, Medicare Part D is a subtle form of price control; the mechanism of price control being competition. The US government reported that during the 2007 bidding process, strong competitive pressure among providers had led to lower costs of coverage by 10 percent less than in 2006. It is clear this competitive factor has indirectly achieved certain price control effects.

Summary

The global pharmas are standing at a paradoxical cross-roads in seeing their future development. On the one hand, they have never enjoyed such heights of profit splendor in their development; on the other hand, they have never faced so much criticism of their business strategy. This criticism reflects the question of the values of medicine in two divergent realities, the business reality and the global health reality. On the one hand, the global pharmaceutical industry is a formidable sector of the economy that has also created other sub-economies. But, on the other hand, they have made important contributions to the saving of lives in the world. Outsiders, though, also believe that the industry's contribution has been handsomely rewarded by their innovations as well as by their aggressive business strategies.

However, outsiders/critics were also concerned about the consequences of these strategies and have taken actions to force the industry to address them. Critics in the United States have generated a long list of what they

believe are major challenges from the industry to health care in the United States and the world. For example, they alleged that the pharmaceutical companies were "illegally overcharging Medicaid and Medicare, paying kickbacks to doctors, engaging in anti-competitive practices, colluding with generic companies to keep generic drugs off the market, illegally promoting drugs for unproved uses, engaging in misleading direct-to-consumer advertising, and ... covering up evidence ... ." And these accusations can go on and on (Angell, 2004, p. 19).

The critics see these revelations as the coming of a perfect storm that could effect the positive development of the industry. The possible consequences could be decrease in innovative output, increase in measures of price controls, cross-border trade, state demand for drug discounts, and increasing demand to reform the current intellectual property rights regime (see related discussions in Martinez and Goldstein, 2007).

Some local governments in the United States have taken action to reduce pharmaceutical spending and this is likely to have an impact on the bottom line of the pharmaceutical sector. In 2003, the governors of Minnesota, Illinois, Iowa, and Wisconsin expressed that they intended to import cheaper medicines from Canada in order to save state budgets, and millions of US dollars for their citizens in the process (Harris, 23 October 2003, "Cheap drugs from Canada"). At the same time, the Illinois democratic governor, Rod R. Blagojevich, supported an online petition to persuade federal officials to allow drug imports. Governor Blagojevich said that millions of US dollars could have been saved from the US$340 million spent in 2002 on prescription drugs for 230,000 Illinois state employees and retirees if Illinois imported drugs from Canada (ibid.). By 2002, the Mayor of Springfield, Massachusetts, had offered city employees a health plan for purchasing their prescription drugs from a Canadian pharmacy and he believed that it would save $9 million of city expenditure. The city of Boston also planned to follow in the footsteps of Springfield, and these developments have also attracted interest from other states.

The measure taken by Maine aroused the most attention. Maine was the first state to pass the "Maine Rx" law, allowing the state to bargain with the pharmas for lower prices for the uninsured (see Pear, 25, December, 2002; see also Denning, 2003). The state threatened to cap the prices or exclude the drugs from the state's formularies. The phramas went to the Supreme Court in 2003, but the Supreme Court refused to review the matter and sent the case back to the lower courts. Maine's action, which reflected a realistic concern for the budgetary

bottom line facing most of the state governments, was supported by 28 other states.

It was noted that the public had also expressed their discontent with the pharmas and their efforts have brought about some results (see the evidence in Angell, 2004). It was observed that the industry has faced a tidal wave of investigations and lawsuits, such as defrauding Medicare or Medicaid by billing for inflated prices, anti-competitive practices, and marketing drugs for unapproved uses. In addition, critics also highlighted the fact that consumer and activist groups were gathering their ammunition to fight against high prices. For example, the Prescription Access Litigation Project, whose goal is to make prescription drug prices more affordable for consumers, has resorted to the use of class action litigation and public education to bring about changes. They have challenged illegal pricing tactics and deceptive marketing by drug companies, Pharmacy Benefit Managers, and other pharmaceutical industry players that fail to pass on savings to consumers or health plans (Prescription Access Litigation, 2007). In early 2002, the public backlash had forced eight companies to pay a total of $2.2 million in fines and settlements (Angell, 2004).

In the face of these criticisms, the global pharmas have provided their responses and their responses also reflect some truths about the business world in which they operate. They have continued to point out that the large pharmas operate in a market-driven framework, in which profit returns are the guiding principle of its operation. It is also true that they have to answer to their investors and maximize the value of their stocks and that their investors include a large number of citizens with pension plans vested in the global pharmas' development (see related arguments in Angell, 2004).

Given these criticisms and counter-criticisms, those who are concerned about population health raise the question: what is the solution then? Or is there a solution at all? Chapter 4 will provide an answer to this question by presenting a contrast between a planting strategy and a plucking strategy in global pharmaceutical development. First, though, Chapter 3 looks at the role of BRICA in the global provision of pharmaceuticals.